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Dated 20 July 2004

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Request for grant of a patent

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The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference	N.88818 GCW/RCS	
2. Patent application number *(The Patent Office will fill in this part)*	0315872.2	-7 JUL 2003
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Ionix Pharmaceuticals Limited 185 Cambridge Science Park Milton Road Cambridge, CB4 0GA	
Patents ADP number *(if you know it)*		
If the applicant is a corporate body, give the country/state of its incorporation	8304891001	
4. Title of the invention	CHEMICAL COMPOUNDS	
5. Name of your agent *(if you have one)*	J.A. KEMP & CO.	
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	14 South Square Gray's Inn London WC1R 5JJ	
Patents ADP number *(if you know it)*	26001	

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing *(day / month / year)*
8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body. See note (d))*	Yes	

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	77
Claim *(s)*	6 DL
Abstract	2
Drawing *(s)*	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1 ✓
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature J. A. Kemp & Co

J.A. KEMP & CO.

Date 7 July 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

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b) *Write your answers in capital letters using black ink or you may type them.*

c) *If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.*

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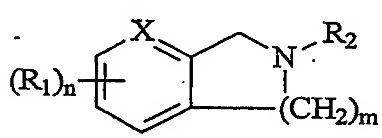
CHEMICAL COMPOUNDS

The present invention relates to inhibitors of the subtype of mammalian sodium channels known as $Na_v1.8$ or sensory neurone specific (SNS) channels. The $Na_v1.8$ channel is a 1,957 amino acid tetrodotoxin-insensitive voltage-gated sodium channel. The sodium channel, nucleic acid sequences coding for the channel, vectors, host cells and methods of identifying modulators, are taught in US-A-6451554. The α-subunit gene corresponding to this ion channel is referred to as SCN10A. The channel is described in more detail in Akopian *et al.*, (1996), 379, 257-262.

Mammalian ion channels are becoming increasingly well characterized, and progress in sodium channel research has been summarized recently in Anger *et al*, J. Med. Chem. (2001) 44, 115-137. Sodium channels are recognised as valid targets for pain therapeutics, and blockade of sodium channels can be useful in the treatment of a range of pain syndromes (see for example Black *et al*, Progress in Pain Research and Management (2001), 21(Neuropathic Pain: Pathophysiology and Treatment), 19-36).

It has now surprisingly been found that compounds of the general formula (I) set out below act as inhibitors of sensory neurone specific sodium channels. Accordingly, the present invention provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof,



(I)

wherein:

- X is -N- or -CH-;
- n is from 0 to 3;
- each R_1 is the same or different and is a hydroxy, amino, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkylthio, (C_1C_6 alkyl)amino or di(C_1-C_6 alkyl)amino group;

- m is 1, 2 or 3; and
- R_2 is either

(a) -L-A, wherein L is a direct bond or a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety and A is C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group or a 5- to 10- membered heterocyclic group,

(b) -L-CR(A)$_2$ or -L-CH=C(A)$_2$ wherein R is hydrogen or C_1-C_4 alkyl, L is as defined above and each A is the same or different and is as defined above,

(c) -L$'$-Het-A$'$, wherein Het is -O-, -S- or -NR$'$-, A$'$ is -L-A, -L-CR(A)$_2$ or -L-CH=C(A)$_2$, R$'$ is H or -L-A, L$'$ is a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety, L is as defined above, R is as defined above and each A is the same or different and is as defined above,

(d) -L-CO-NR$_3$R$_4$ or -L-CS-NR$_3$R$_4$, wherein L is as defined above and either (i) R_3 and R_4, together with the N atom to which they are attached, form a 5- to 10- membered heteroaryl or heterocyclyl group or (ii) R_3 represents -L-H or A$'$ wherein L and A$'$ are as defined above, and R_4 represents -L$'$-H, -L$'$-CO-A, A$'$, -L-CR(LA)$_2$ or -L-CH=C(LA)$_2$ wherein each L is the same or different, each A is the same or different, and L$'$, L, R, A and A$'$ are as defined above,

(e) -CO-L-NR$_3$R$_4$ or -CS-L-NR$_3$R$_4$ wherein L, R_3 and R_4 are as defined above,

(f) -CO-A$'$ or -CS-A$'$ where A$'$ is as defined above, or

(g) -L$'$-O-N=C(A)$_2$ or -CO-L$'$-O-N=C(A)$_2$ wherein L$'$ is as defined above and each A is the same or different and is as defined above;

wherein

- said aryl, carbocyclyl, heteroaryl and heterocyclyl groups are optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6- membered heterocyclyl and heteroaryl groups, and
- said aryl, heteroaryl, carbocyclyl and heterocyclyl groups are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and -CHPh$_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 halogen atoms.

As used herein, a C_1-C_6 alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as C_1-C_4 alkyl group or

moiety, for example methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl. A divalent alkyl moiety (or alkylene moiety) can be attached via the same carbon atom, by adjacent carbon atoms or by non-adjacent carbon atoms.

As used herein, a C_2-C_6 alkenyl group or moiety is a linear or branched alkenyl group or moiety containing from 2 to 6 carbon atoms, such as a C_2-C_4 alkenyl group or moiety, for example ethenyl, propenyl and butenyl. Typically, an alkenyl group or moiety is saturated except for one double bond. A divalent alkenyl moiety (or alkenylene moiety) can be attached via the same carbon atoms, via adjacent carbon atoms or via non-adjacent carbon atoms.

As used herein, a C_2-C_6 alkynyl group or moiety is a linear or branched alkynyl group or moiety containing from 2 to 6 carbon atoms, such as a C_2-C_4 alkynyl group or moiety, for example ethynyl, propynyl and butynyl. Typically, an alkynyl group or moiety is saturated except for one triple bond. A divalent alkynyl moiety (or alkynylene moiety) can be attached via the same carbon atom, via adjacent carbon atoms or via non-adjacent carbon atoms.

As used herein, a C_6-C_{10} aryl group or moiety is typically a phenyl or naphthyl group or moiety. It is preferably a phenyl group or moiety.

As used herein, a 5- to 10- membered heteroaryl group is a 5- to 10-membered aromatic ring, such as a 5- or 6- membered ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, imidazolyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, isoxazyl, thiadiazolyl, thiazolyl and pyrazolyl groups. Thienyl, triazolyl, pyridyl, thiazolyl and imidazolyl groups are preferred.

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine and is preferably chlorine or fluorine. As used herein, a said C_1-C_6 alkoxy group is typically a said C_1-C_6 alkyl group attached to an oxygen atom. A said C_1-C_6 alkylthio group is typically a said C_1-C_6 alkyl group attached to a thio group.

As used herein, a C_1-C_6 haloalkyl group is typically a said C_1-C_6 alkyl group, for example a C_1-C_4 alkyl group, substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl groups include perhaloalkyl groups such as $-CX_3$ wherein X is a said halogen atom. Particularly preferred haloalkyl groups are $-CF_3$ and $-CCl_3$.

As used herein, a C_1-C_6 haloalkoxy group is typically a said C_1-C_6 alkoxy group, for example a C_1-C_4 alkoxy group, substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkoxy groups include perhaloalkoxy groups such as $-OCX_3$ wherein X is a said halogen atom. Particularly preferred haloalkoxy groups are $-OCF_3$ and $-OCCl_3$.

As used herein, a C_1-C_6 haloalkylthio group is typically a said C_1-C_6 alkylthio group, for example a C_1-C_4 alkylthio group, substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkylthio groups include perhaloalkylthio groups such as $-SCX_3$ wherein X is a said halogen atom. Particularly preferred haloalkylthio groups are $-SCF_3$ and $-SCCl_3$.

As used herein, a C_3-C_6 carbocyclyl group or moiety is a non-aromatic saturated or unsaturated hydrocarbon ring, having from 3 to 6 carbon atoms. Preferably it is a saturated group, i.e. a C_3-C_6 cycloalkyl group. Examples include cyclobutyl, cyclopentyl and cyclohexyl.

As used herein, a 5- to 10- membered heterocyclyl group or moiety is a non-aromatic, saturated or unsaturated C_5-C_{10} carbocyclic ring in which one or more, for example 1, 2 or 3, of the carbon atoms are replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are preferred. Examples of suitable heterocyclyl groups include piperidinyl, piperazinyl, morpholinyl, pyrrolidinyl, tetrahydrofuranyl, imidazolidinyl, thiazolidinyl, 1,4 dioxanyl, 1,3 dioxolanyl and homopiperidinyl groups. Preferred heterocyclyl groups are piperidinyl, morpholinyl, piperazinyl and homopiperidinyl groups.

Typically, the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_2, R_3 and R_4 are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and $-CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 halogen atoms. Preferably, the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_2, R_3 and R_4 are unsubstituted or are substituted by 1 or 2 substituents which are the same or different and are selected from halogen, C_1-C_2 alkyl, hydroxy, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2

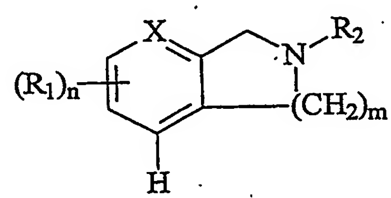
haloalkylthio, phenyl and $-CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 further substituents selected from fluorine and chlorine atoms.

Typically, X is -CH-.

Typically, n is 0 or 1.

Preferably, each R_1 is the same or different and is a hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio or C_1-C_4 haloalkylthio group. More preferably, each R_1 is the same or different and is C_1-C_2 alkyl, hydroxy or C_1-C_2 alkoxy.

Typically R_1 is located meta to the fused heterocycle, or on the phenyl carbon atom nearest the N atom. Thus, the compound of formula (I) is typically a compound of formula



Typically, each L moiety in the R_2 substituent is the same or different and represents a direct bond or a C_1-C_6 alkyl moiety. Preferably, each L is the same or different and represents a direct bond or a C_1-C_4 alkyl moiety, for example a methyl, ethyl or propyl moiety, for example $-CH(CH_2)-$ or $-CH_2-CH(CH_3)-$.

Typically each L' moiety in the R_2 substituent is the same or different and represents a C_1-C_6 alkyl moiety, preferably a C_1-C_4 alkyl moiety, for example a methyl, ethyl or propyl moiety, for example $-CH(CH_2)-$ or $-CH_2-CH(CH_3)-$.

Typically, each A moiety in the R_2 substituent is the same or different and represents a C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 5- or 6- membered heterocyclyl or 5- or 6- membered heteroaryl group, which group is (a) unsubstituted or substituted by 1, 2 or 3 substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and halophenyl substituents and (b) optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6- membered heterocyclyl or heteroaryl groups.

More typically, each A moiety in the R_2 substituent is the same or different and is a phenyl, thienyl, triazolyl, pyridyl, cyclopentyl, imidazolyl, thiazolyl or piperidyl group which is (a) unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio, phenyl, C_1-C_2 alkyl, C_1-C_2 alkoxy and hydroxy groups and (b) optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6- membered heteroaryl moieties.

Preferably, each A moiety in the R_2 substituent is a phenyl, thienyl, triazolyl, pyridyl, fluorenyl, thiazolyl, tetrahydroisoquinolinyl or benzimidazolyl group, which group is unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_2 alkyl, hydroxy, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio and phenyl substituents.

Typically, each R substituent in each $-CR(A)_2$ moiety is the same or different and is hydrogen or methyl.

Typically, each Het moiety in the R_2 substituent is -O-, -S- or $-NR'-$ wherein R' is hydrogen, C_1-C_4 alkyl, phenyl or -(C_1-C_4 alkyl)-phenyl. More preferably, each Het moiety in the R_2 substituent is -O- or $-NR'-$ wherein R' is hydrogen, C_1-C_4 alkyl or benzyl.

Typically, when R_3 and R_4, together with the N atom to which they are attached, form a heterocycle, they form a 5- to 7- membered heterocyclyl group. Preferably, they form a morpholino, piperazinyl or homopiperidinyl ring which is (a) unsubstituted or substituted by 1 or 2 substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, phenyl and $-CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 halogen atoms and (b) optionally fused to one or two phenyl rings.

Typically, when R_3 and R_4 do not together form a heterocycle, R_3 represents hydrogen, C_1-C_4 alkyl, -(C_1-C_4 alkyl)-phenyl or -(C_1-C_4 alkyl)-$CHPh_2$. Preferably, R_3 is unsubstituted. Most preferably, R_3 represents hydrogen, C_1-C_4 alkyl or an unsubstituted benzyl or -(C_1-C_2 alkyl)-$CHPh_2$ group.

Typically, when R_3 and R_4 do not together form a heterocycle, R_4 represents C_1-C_4 alkyl, A, -(C_1-C_4 alkyl)-A, $-(CH_2)_m-CH(A)_2$, $-CH[(CH_2)_mA]_2$ or $-(CH_2)_m-CO-A$ wherein each A is the same or different and is as defined above and m is 0, 1, 2, 3 or 4.

Preferably, the A moieties in the R_4 substituent are (a) unsubstituted or substituted by 1 or 2 substituents selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents and (b) monocyclic or fused to 1 or 2 phenyl rings.

Most preferably, when R_3 and R_4 do not together form a heterocycle, R_4 represents C_1-C_4 alkyl, fluorenyl, -(C_1-C_4 alkyl)-phenyl, -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), $-(CH_2)_m-CHA''A'''$ wherein m is 0, 1, 2 or 3 and A'' and A''' are the same or different and each represent phenyl or a 5- or 6- membered heteroaryl group, $-CH[(CH_2)_nPh]_2$ wherein n is 0, 1 or 2, or $-(CH_2)_p-CO-R$ wherein p is 1, 2 or 3 and R is a 5- or 6- membered heterocyclic group fused to a phenyl ring, for example a tetrahydroisoquinoline group, the cyclic moieties in said most preferred R_4 groups being unsubstituted or substituted by a halogen atom, C_1-C_2 alkyl or C_1-C_2 alkoxy group.

Typically, when R_2 is defined according to option (a), L is C_1-C_4 alkyl and A is a phenyl or 5- or 6- membered heteroaryl group, which group is unsubstituted or substituted by 1, 2 or 3 substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and halophenyl substituents.

Preferably, when R_2 is defined according to option (a), it is a -(C_1-C_4 alkyl)-phenyl group, for example benzyl, or a -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl) group, for example $-CH_2$-thienyl or $-CH_2$-triazolyl, the phenyl and heteroaryl moieties being unsubstituted or substituted by 1 or 2 substituents selected from C_1-C_2 haloalkyl, halogen, C_1-C_2 haloalkylthio, C_1-C_2 haloalkoxy, C_1-C_2 alkyl and phenyl substituents.

Typically, when R_2 is defined according to option (b), it is $-L-CR(A)_2$ wherein R and A are as defined above. Preferably, L is C_1-C_4 alkyl, R is hydrogen or methyl and each A is the same or different and is a phenyl group which is unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C_1-C_2 haloalkyl, C_1-C_2 alkyl and hydroxy substituents.

Typically, when R_2 is defined according to option (c), L' is C_1-C_4 alkyl, Het is O, NH or -N(benzyl)- and A' is an unsubstituted -(C_1-C_4)alkyl-phenyl, -(C_1-C_4 alkyl)-$CHPh_2$ or $-CH{=}CHPh_2$ group.

Typically, when R_2 is defined according to option (d), L is other than a direct bond. More typically, L is C_1-C_6 alkyl.

Further, when R_2 is defined according to option (d), it is typically -L-CO-NR_3R_4. More typically, when R_2 is defined according to option (d), R_2 is -$(CH_2)_q$-CO-NR_3R_4 wherein q is from 1 to 4, and is preferably 1 or 2, and R_3 and R_4 are as defined above. Preferably, when R_2 is defined according to option (d), either (i) R_3 and R_4, together with the N atom to which they are attached, form a 5- to 7-membered heterocyclyl group or (ii) R_3 represents hydrogen, C_1-C_4 alkyl or -(C_1-C_4 alkyl)-phenyl and R_4 represents C_1-C_4 alkyl, A, -(C_1-C_4 alkyl)-A, -$(CH_2)_m$-CH$(A)_2$ or -CH$[(CH_2)_mA]_2$ wherein each A is the same or different and is as defined above and m is 0, 1, 2, 3 or 4.

More preferably, when R_2 is defined according to option (d) either (i) R_3 and R_4, together with the N atom to which they are attached, form a morpholino, piperazinyl or homopiperdinyl ring which is (a) unsubstituted or substituted by 1 or 2 substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, phenyl and -$CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 halogen atoms and (b) optionally fused to one or two phenyl rings or (ii) R_3 represents hydrogen, C_1-C_4 alkyl or an unsubstituted benzyl group and R_4 represents C_1-C_4 alkyl, fluorenyl, -(C_1-C_4 alkyl)-phenyl, -(C_1-C_6 alkyl)-(5- to 6- membered heteroaryl), -$(CH_2)_m$CH$A''A'''$ wherein m is 0, 1, 2 or 3 and A'' and A''' are the same or different and each represent phenyl or a 5- or 6- membered heteroaryl group, or -CH$[(CH_2)_nPh]_2$ wherein n is 0, 1 or 2, the cyclic moieties in these groups being unsubstituted or substituted by a C_1-C_2 alkyl group.

Typically, when R_2 is defined according to option (e), L is a direct bond or a C_1-C_4 alkyl moiety, for example a methyl moiety, and R_3 and R_4 are as defined above.

Typically, when R_2 is defined according to option (f), it is -CO-A'. More typically, when R_2 is defined according to option (f), it is -CO-L-CH$(A)_2$ or -CO-L-A, wherein L is as defined above and each A is the same or different and is as defined above.

Preferably, when R_2 is defined according to option (f), it is -CO-CH_2-CH$(R)_2$ or -CO-R', wherein each R is the same or different and is a phenyl or halophenyl moiety and R' is a benzimidazolyl group.

Typically, when R_2 is defined according to option (g), it is $-CO-L'-O-N=C(A)_2$, wherein L' is as defined above and each A is the same or different and is as defined above. Preferably, when R_2 is defined according to option (g), it is $-CO-CH_2-O-N=CR''R'''$ wherein R'' and R''' are the same or different and each represent an unsubstituted phenyl or pyridyl group.

Preferred compounds of formula (I) are those in which:

- X is -CH-;
- n is from 0 to 3;
- m is 1, 2 or 3;
- each R_1 is the same or different and is a hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, or C_1-C_4 haloalkylthio group; and
- R_2 is either

(a) -L-A wherein L is a direct bond or a C_1-C_6 alkyl moiety and A is a C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 5- or 6- membered heterocyclyl or 5- or 6- membered heteroaryl group,

(b) $-L-CR(A)_2$ or $-L-CH=C(A)_2$ wherein R is hydrogen or C_1-C_4 alkyl, L is as defined above and each A is the same or different and is as defined above,

(c) $-L'-Het-A'$, wherein Het is -O-, -S- or $-NR'-$ wherein R' is hydrogen, C_1-C_4 alkyl, phenyl or -(C_1-C_4 alkyl)-phenyl, A' is -L-A, $-L-CR(A)_2$ or $-L-CH=C(A)_2$, L' is a C_1-C_6 alkyl moiety, L is as defined above and each A is the same or different and is as defined above,

(d) $-L-CO-NR_3R_4$ or $-L-CS-NR_3R_4$ wherein L is as defined above and either (i) R_3 and R_4, together with the nitrogen atom to which they are attached, form a 5- to 7- membered heterocyclyl group or (ii) R_3 represents hydrogen, C_1-C_4 alkyl, -(C_1-C_4 alkyl)-phenyl or -(C_1-C_4 alkyl)-$CHPh_2$ and R_4 represents C_1-C_4 alkyl, A, -(C_1-C_4 alkyl)-A, $-(CH_2)_m-CH(A)_2$, $-CH[(CH_2)_mA]_2$ or $-(CH_2)_m-CO-A$ wherein each A is the same or different and is as defined above and m is 0, 1, 2, 3 or 4,

(e) $-CO-L-NR_3R_4$ or $-CS-L-NR_3R_4$ wherein L, R_3 and R_4 are as defined above,

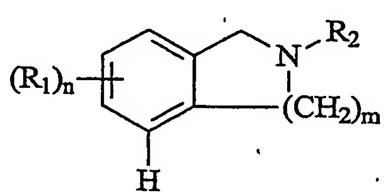
(f) $-CO-A'$ or $-CS-A'$ wherein A' is as defined above, or

(g) -L′-O-N=C(A)$_2$, -CO-L′-O-N=C(A)$_2$ wherein L′ is as defined above and each A is the same or different and is as defined above,

wherein

- said aryl, heteroaryl, carbocyclyl and heterocyclyl groups are optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6- membered heterocyclyl and heteroaryl groups, and
- said aryl, heteroaryl, carbocyclyl and heterocyclyl groups are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and -CHPh$_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by one or two halogen atoms.

Most preferred compounds of formula (I) are compounds of formula (Ia)



(Ia)

wherein

- n is 0 or 1;
- each R$_1$ is the same or different and is C_1-C_2 alkyl, hydroxy or C_1-C_2 alkoxy;
- m is 1, 2 or 3; and
- R$_2$ is either

(a) -L-A wherein L represents a direct bond or a C_1-C_4 alkyl moiety, for example a methyl, ethyl or propyl moiety, and A is a phenyl, thienyl, triazolyl, pyridyl, fluorenyl, thiazolyl, tetrahydroisoquinolinyl or benzimidazolyl group, which group is unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_2 alkyl, hydroxy, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio and phenyl substituents,

(b) -L-CR(A)$_2$ or -L-CH=C(A)$_2$ wherein R is hydrogen or methyl, L is as defined above and each A is the same or different and is as defined above,

(c) $-L'$-Het-A' wherein Het is -O- or $-NR'$- wherein R' is hydrogen, C_1-C_4 alkyl or benzyl, A' is -L-A, -L-CR(A)$_2$ or -L-CH=C(A)$_2$, L' is a C_1-C_4 alkyl moiety, for example a methyl, ethyl or propyl moiety, L is as defined above, R is as defined above and each A is the same or different and is as defined above,

(d) -L-CO-NR_3R_4 wherein L is as defined above and either (i) R_3 and R_4, together with the nitrogen atom to which they are attached, form a morpholino, piperazinyl or homopiperidinyl ring which is (a) substituted or unsubstituted by one or two substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, phenyl and -$CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by one or two halogen atoms and (b) optionally fused to one or two phenyl rings, or (ii) R_3 represents hydrogen, C_1-C_4 alkyl or an unsubstituted benzyl or -CH_2-CH_2-$CHPh_2$ group and R_4 represents C_1-C_4 alkyl, fluorenyl, -(C_1-C_4 alkyl)-phenyl, -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), -$(CH_2)_m$-$CHA''A'''$ where m is 0, 1, 2 or 3 and A'' and A''' are the same or different and each represent phenyl or a 5- or 6- membered heteroaryl group, -$CH[(CH_2)_nPh]_2$, wherein n is 0, 1 or 2, or -$(CH_2)_p$-CO-R wherein p is 1, 2 or 3 and R is 5- or 6- membered heterocyclic group fused to a phenyl ring, for example a tetrahydroisoquinoline group, the cyclic moieties in said R_4 groups being unsubstituted or substituted by a halogen atom, C_1-C_2 alkyl or C_1-C_2 alkoxy group,

(e) -CO-L-NR_3R_4 or -CS-L-NR_3R_4 wherein L, R_3 and R_4 are as defined above,

(f) -CO-A' or CS-A' wherein A' is as defined above, or

(g) -CO-L'-O-N=C(A)$_2$ wherein L' is as defined above and each A is the same or different and is as defined above.

Examples of these particularly preferred compounds of the invention include:

2-(3,5-bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-ol
2-(2-chloro-6-fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol
2-(2,5-difluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol
2-(3,5-difluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol
2-(4-trifluoromethylsulfanyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol
2-(3,5-bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol
2-(2-dibenzylamino-ethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-[4,4-bis-(4-fluoro-phenyl)-butyl]-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-[4,4-bis-(4-hydroxy-3,5-dimethyl-phenyl)-pentyl]-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone

2-(2-benzyloxy-propyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(2,2-diphenyl-ethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

N-benzhydryl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-(9H-fluoren-9-yl)-acetamide

N-(1-benzyl-2-phenyl-ethyl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-(1,2-diphenyl-ethyl)-acetamide

2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-(3,3-diphenyl-propyl)-acetamide

N-benzhydryl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(9H-fluoren-9-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-benzyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide

N-(3,3-diphenyl-propyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-dibenzyl-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

2-thiophen-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ol

N-benzhydryl-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-benzyl-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide

N-(9H-fluoren-9-yl)-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(3,3-diphenyl-propyl)-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

2-(5-phenyl-2H-[1,2,3]triazol-4-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

1-(3,4-dihydro-1H-isoquinolin-2-yl)-2-(2,2-diphenyl-ethylamino)-ethanone

1-(3,4-dihydro-1H-isoquinolin-2-yl)-2-(3,3-diphenyl-propylamino)-ethanone

1-(3,4-dihydro-1H-isoquinolin-2-yl)-2-[[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-(3,3-diphenyl-propyl)-amino]-ethanone

2-dibenzylamino-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

N-(3,3-diphenyl-propyl)-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-dibenzyl-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

dibenzyl-[2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine

2-(2,2-diphenyl-ethyl)-1,2,3,4-tetrahydro-isoquinoline

2-(2,2-diphenyl-ethyl)-8-methoxy-1,2,3,4-tetrahydro-isoquinoline

2-[4,4-bis-(4-fluoro-phenyl)-butyl]-1,2,3,4-tetrahydro-isoquinoline
2-[4,4-bis-(4-fluoro-phenyl)-butyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline
1-(3,4-dihydro-1H-isoquinolin-2-yl)-3,3-bis-(4-fluoro-phenyl)-propan-1-one
2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-[1-(5-methyl-thiazol-2-yl)-ethyl]-acetamide
2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-[1-(5-methyl-thiazol-2-yl)-ethyl]-acetamide
(3,3-diphenyl-propyl)-[2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine
2-(benzhydryl-amino)-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
dibenzyl-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine
[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-(3,3-diphenyl-propyl)-amine
2-{(2,2-diphenyl-ethyl)-[2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-amino}-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
2-{benzhydryl-[2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-amino}-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
2-(benzhydryl-amino)-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
2-(2,2-diphenyl-ethylamino)-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
(1H-benzoimidazol-5-yl)-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone
N-(2,2-diphenyl-ethyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide
1-(4-benzhydryl-piperazin-1-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
1-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
1-(4-benzhydryl-piperazin-1-yl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
1-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
2-(1,3-dihydro-isoindol-2-yl)-N-(2,2-diphenyl-ethyl)-acetamide
1-(4-benzhydryl-piperazin-1-yl)-2-(1,3-dihydro-isoindol-2-yl)-ethanone
1-{4-[bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(1,3-dihydro-isoindol-2-yl)-ethanone
2-benzhydrylideneaminooxy-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone
2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-(2,2-diphenyl-ethyl)-acetamide
2-(1,3-dihydro-isoindol-2-yl)-N-(3,3-diphenyl-propyl)-acetamide

N-(3,3-diphenyl-propyl)-3-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propionamide

2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(phenyl-pyridin-2-yl-methyl)-acetamide

3,4-dihydro-1H-isoquinoline-2-carbothioic acid (2,2-diphenyl-ethyl)-amide

N-benzhydryl-2-(1,3-dihydro-isoindol-2-yl)-acetamide

3,4-dihydro-1H-isoquinoline-2-carbothioic acid benzhydryl-amide

8-methoxy-3,4-dihydro-1H-isoquinoline-2-carbothioic acid benzhydryl-amide

8-methoxy-3,4-dihydro-1H-isoquinoline-2-carbothioic acid (2,2-diphenyl-ethyl)-amide

2-benzhydrylideneaminooxy-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2-(di-pyridin-2-yl-methyleneaminooxy)-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone

2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-phenoxazin-10-yl-ethanone

1-(10,11-dihydro-dibenzo[b,f]azepin-5-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2-[3-(2,2-diphenyl-vinyloxy)-propyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline

4-methoxy-1,3-dihydro-isoindole-2-carbothioic acid benzhydryl-amide

7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepine-2-carbothioic acid benzhydryl-amide

7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepine-2-carbothioic acid (2,2-diphenyl-ethyl)-amide

N,N-diisopropyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-dibenzyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-benzhydryl-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide

N-(4,4-diphenyl-butyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(4,4-diphenyl-butyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide

N-benzhydryl-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide

N-(2,2-diphenyl-ethyl)-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide

N-(3,3-diphenyl-propyl)-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide
N,N-dibenzyl-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide
N,N-dibenzyl-3-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propionamide
N-(3,3-diphenyl-propyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide
N-(2,2-diphenyl-ethyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide
2-(1,3-Dihydro-isoindol-2-yl)-N-(2,2-diphenyl-ethyl)-acetamide
and pharmaceutically acceptable salts thereof.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

The compounds of the invention can contain one or more chiral centre. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereoisomers of the compounds shown, including racemic and non-racemic mixtures and pure enantiomers and/or diastereoisomers.

Preferred compounds of the invention are optically active isomers. Thus, for example, preferred compounds of formula (I) containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer.

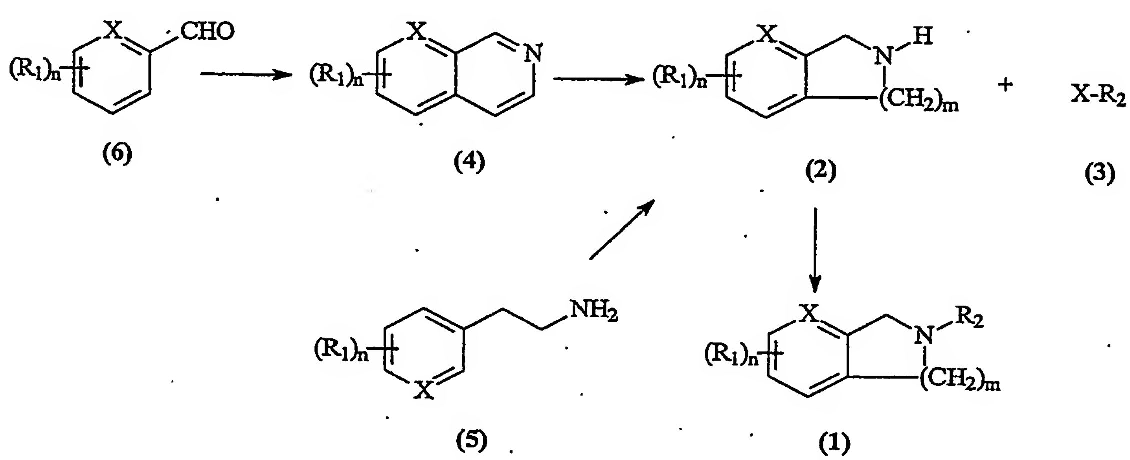
The compounds of formula (I) may be prepared by conventional routes, for example those set out in any of schemes 1 to 10 shown below.

Compounds of formula (1) in which m is 2 and X, R_1, n and R_2 are defined as above (reaction scheme 1) may be prepared from compounds of formula (2) and compounds of formula (3) where X is a leaving group, typically chlorine, using standard methods such as reaction in the presence of a base, for example potassium carbonate. Typically the reaction is performed in a solvent such as methanol,

tetrahydrofuran or acetonitrile at a temperature of 95°C. Compounds of formula (2) may be prepared from compounds of formula (4) by standard methods familiar to those skilled in the art such as reduction in the presence of platinum oxide. Alternatively, compounds of formula (2) may be prepared from compounds of formula (5) and formaldehyde by standard methods such as the Pictet-Spengler cyclisation.

Compounds of formula (4) are known compounds or may be prepared by standard methods such as cyclisation of compounds of formula (6) according to the published procedure Bioorg. Med. Chem. 7 (1999) 2647-2666.

Scheme 1

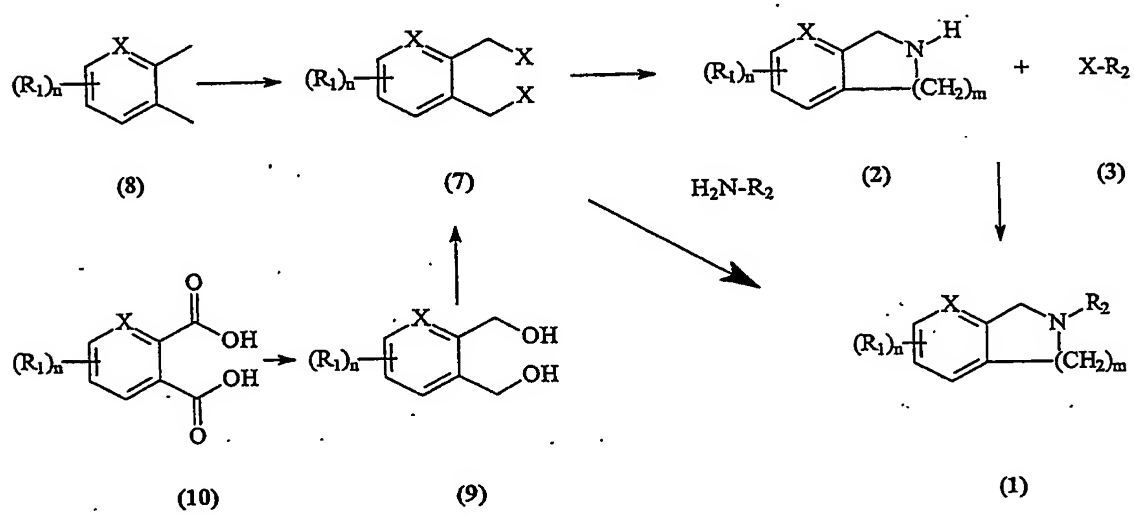


Compounds of formula (1) in which m is 1 and X, R_1, n and R_2 are defined as above (reaction scheme 2) may be prepared from compounds of formula (2) and compounds of formula (3) where X is a leaving group, typically chlorine, using standard methods such as reaction in the presence of a base for example potassium carbonate. Typically the reaction is performed in a solvent such as methanol, tetrahydrofuran or acetonitrile at a temperature of 95°C.

Compounds of formula (2) may be prepared from compounds of formula (7) where X is a leaving group, preferably bromine, by standard methods familiar to those skilled in the art such as alkylation in the presence of an amine. Alternatively, compounds of formula (2) can be prepared from compounds of formula (7) where X

is OH converted into a better leaving group such as a mesylate under standard alkylating conditions familiar to those skilled in the art. Compounds of formula (7) may be prepared from dimethylaryl compounds (8) by bromination using a brominating reagent, for example N-bromosuccinimide. Alcohols (9) may be prepared from acids (10) by standard methods such as reduction in the presence of lithium aluminium hydride.

Scheme 2

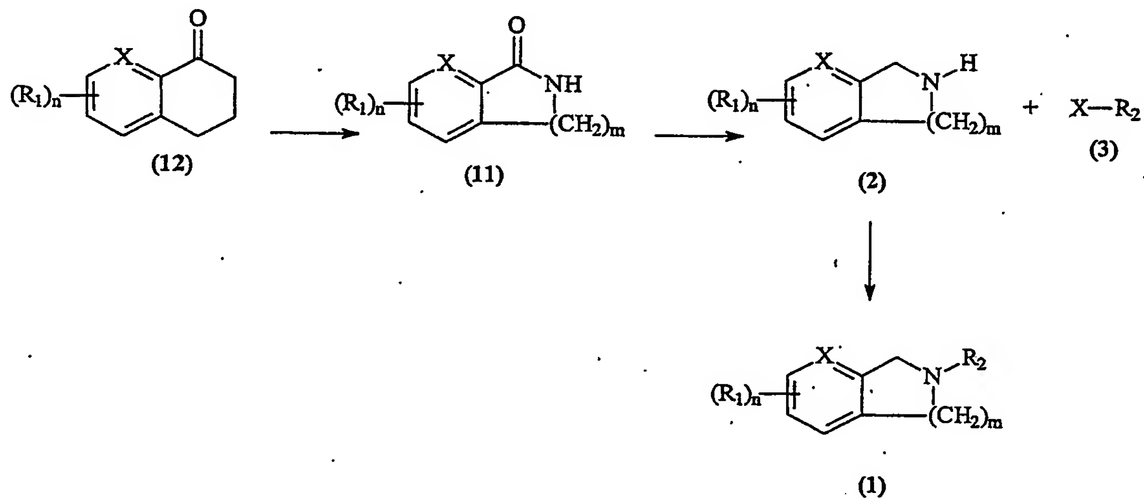


Compounds of formula (I) in which m is 3 and X, R_1, n and R_2 are defined as above (reaction scheme 3) may be prepared from compounds of formula (2) and compounds of formula (3) where X is a leaving group, typically chlorine, using standard methods such as reaction in the presence of a base for example potassium carbonate. Typically the reaction is performed in a solvent such as methanol, tetrahydrofuran or acetonitrile at a temperature of 95°C.

Compounds of formula (2) where m is 3 may be prepared from compounds of formula (11) by reduction in the presence of a metal hydride for example lithium aluminium hydride. Compounds of formula (11) may be prepared from tetralones (12) by standard methods familiar to those skilled in the art such as the Schmidt reaction. Alternatively, compounds of formula (11) may be prepared from tetralones (12) by standard methods familiar to those skilled in the art such as the Beckmann rearrangement or further methods as outlined e.g. in Alicyclic Chemistry, (Martin

Grossel, Oxford University Press). Tetralones (12) are either known compounds or can be prepared by analogy with known methods.

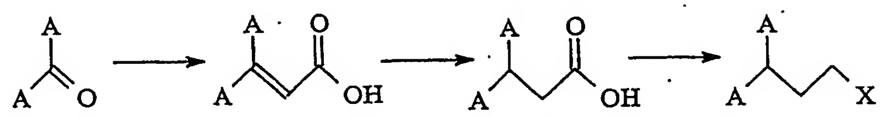
Scheme 3



When R_2 is -L-A and L is other than a direct bond, or when R_2 is –L-CR(A)$_2$, the reaction between the compounds of formulae (2) and (3) in schemes 1, 2 and 3 is typically performed in a solvent such as methanol, tetrahydrofuran or acetonitrile at a temperature of 80°C. When R_2 is -L-A and L is a direct bond, the reaction between the compounds of formulae (2) and (3) is typically effected by Buchwald coupling. Thus, X in the formula (3) is typically bromine or iodine.

The compounds of formula (3) are known compounds, or may be prepared by known methods. For example, compounds of formula (3) in which R_2 is -$(CH_2)_2$-CH$(A)_2$ can be prepared by the reduction of compounds of formula (14) in the presence of a reducing agent such as lithium aluminium hydride followed by halogenation in the presence of a halogenating agent such as PBr_3 (reaction scheme 4). Compounds of formula (14) may be prepared from diarylethenylacids (15) by reduction in the presence of a reducing agent such as palladium. Diarylethenylacids may be prepared from ketones (16) by standard methods familiar to those skilled in the art such as Wittig reaction.

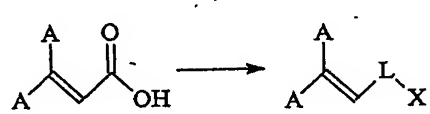
Scheme 4



(16) (15) (14) (13)

Compounds of formula (3) in which R_2 is -L-CH=C(A)$_2$ where L and A are defined as above (reaction scheme 5) may be prepared from corresponding carboxylic acids by reduction in the presence of a reducing agent, for example lithium aluminium hydride, followed by halogenation in the presence of a halogenating reagent for example PBr_3.

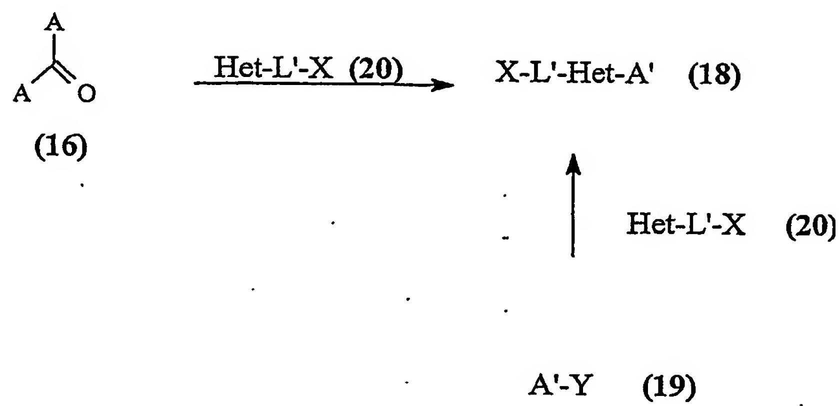
Scheme 5



(15) (17)

Compounds of formula (3) wherein R_2 is -L$'$-Het-A$'$ can, for example, be prepared from compounds of formula (19) where Y is a leaving group, by reaction with compounds of formula (20) (reaction scheme 6). Compounds of formula (18) in which A$'$ is -CH$_2$(A)$_2$ may also be prepared from compounds of formula (16) and compounds of formula (20) by standard methods familiar to those skilled in the art. Thus, when Het is O or S, compounds (16) and (20) can be condensed in the presence of an acid catalyst, for example PTSA. When Het is NH the reaction between compounds (16) and (20) can be effected by standard methods such as reductive amination in the presence of a reducing agent, for example sodium borohydride.

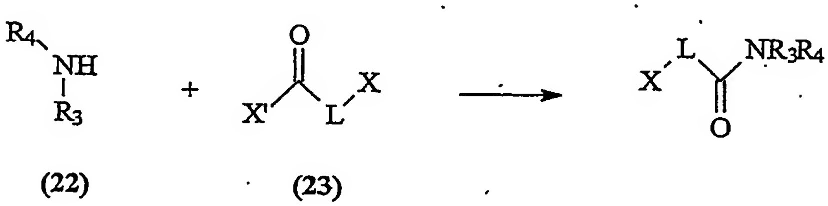
Scheme 6



When R_2 is -L-CO-NR_3R_4 the reaction between the compounds of formulae (2) and (3) in schemes 1 to 3 is typically effected in the presence of a base for example triethylamine. Typically the reaction is performed in a solvent such as methanol, tetrahydrofuran or acetonitrile at a temperature of 80°C. Further, compounds of formula (1) wherein R_2 is -L-CS-NR_3R_4 may be prepared from compounds of formula (1) where R_2 is -L-CO-NR_3R_4 by standard methods familiar to those skilled in the art such as sulphonation in the presence of Lawesson's reagent.

Compounds of formula (3) in which R_2 is -L-CO-NR_3R_4 can be prepared from amines (22) and compounds of formula (23), in which X' is Cl or OH, under standard amide coupling reaction conditions (reaction scheme 7). Typically, where X' is Cl, the reaction is effected in the presence of triethylamine.

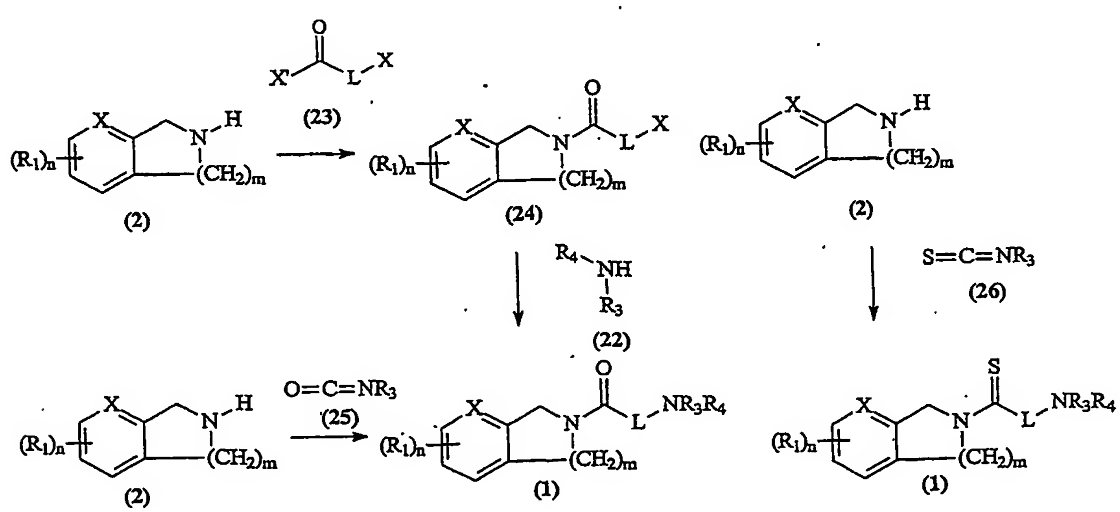
Scheme 7



A further method for preparing compounds of formula (1) wherein X, m, R_1 and n are defined as above and R_2 is -CO-L-NR_3R_4 involves the reaction of amides (24) and amines (22) where X is a leaving group, preferably chlorine, using standard methods such as reaction in the presence of a base for example triethylamine (reaction scheme 8). Typically the reaction is performed in a solvent such as methanol, tetrahydrofuran or acetonitrile at a temperature of 80°C. Amides (24) may be prepared from amines (2) and acids (23), wherein X′ is Cl or OH, under standard amide coupling reaction conditions. Typically, where X′ is Cl, the reaction is effected in the presence of triethylamine.

Alternatively, compounds of formula (1) where R_2 is -CO-L-NR_3R_4, L is a direct bond and R_4 is hydrogen may be prepared from amines (2) by standard methods familiar to those skilled in the art such as alkylation with isocyanates (25). Similarly, compounds of formula (1) where R_2 is -CS-L-NR_3R_4 and L is a direct bond may be prepared from amines (2) by standard methods such as alkylation with isothiocyanates (26). Compounds of formula (1) wherein R_2 is -CS-L-NR_3R_4 can, of course, be prepared from compounds of formula (1) where R_2 is -L-CO-NR_3R_4 by standard methods familiar to those skilled in the art such as sulphonation using Lawesson's reagent.

<u>Scheme 8</u>

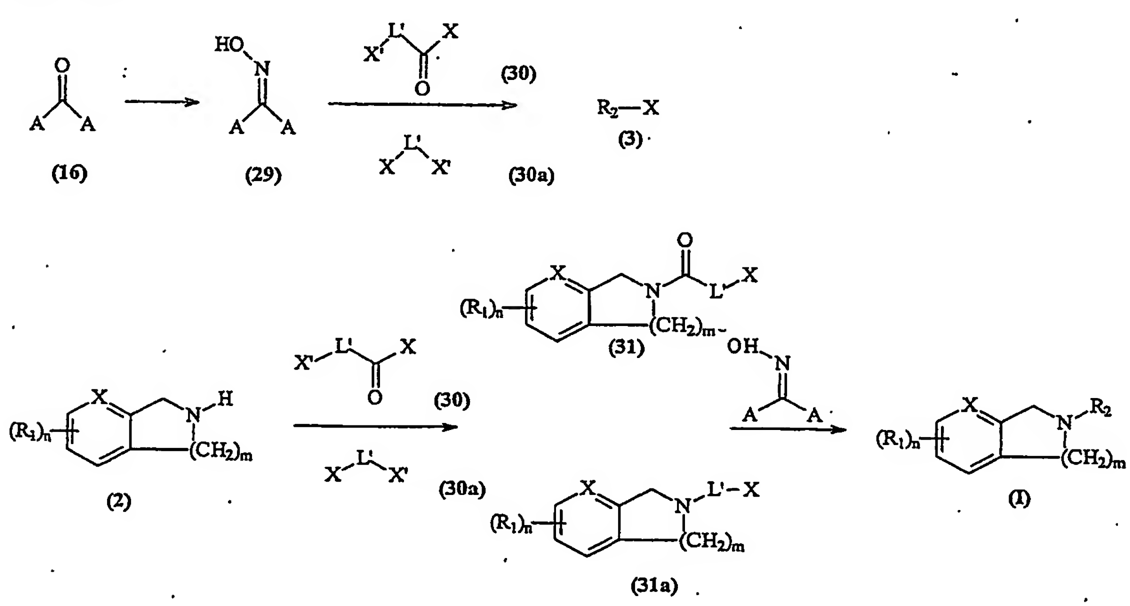


When R_2 is -CO-A$'$, the reaction between the compounds of formulae (2) and (3) in schemes 1, 2 and 3 is typically effected in the presence of a coupling agent such as EDC/HOBT, HATU or HBTU. Compounds of formula (1) wherein R_2 is -CS-A$'$ can, of course, be prepared from compounds of formula (1) where R_2 is -CO-A$'$ by standard methods familiar to those skilled in the art such as reaction with Lawesson's reagent.

Compounds of formula (3), wherein R_2 is -CO-L$'$-O-N=C(A)$_2$ or -L$'$-O-N=C(A)$_2$ may be prepared from ketones (16) and hydroxylamine by standard methods familiar to those skilled in the art (reaction scheme 9). In reaction scheme 9, X and X$'$ represent leaving groups, for example chlorine.

Further, an additional method of preparing compounds of formula (I) in which R_2 is -CO-L$'$-O-N=C(A)$_2$ or -L$'$-O-N=C(A)$_2$ involves the reaction of a compound of formula (31) or (31a), wherein X is a leaving group, typically chlorine, and oximes (29) by standard methods as previously described. Compounds of formulae (31) and (31a) may be prepared from amines (2) and compounds of formulae (30) or (30a) under standard amide coupling conditions as previously described.

<u>Scheme 9.</u>



The compounds of the invention are found to be inhibitors of sensory neurone specific sodium channels. The compounds of the invention are therefore therapeutically useful. Accordingly, the present invention provides a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body. Also provided is a pharmaceutical composition comprising a compound of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent. Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free. Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules. Preferred pharmaceutical compositions of the invention are compositions suitable for oral administration, for example tablets and capsules.

Compositions suitable for oral administration may, if required, contain a colouring or flavoring agent. Typically, a said capsule or tablet comprises from 5 to 500 mg, preferably 10 to 500 mg, more preferably 15 to 100 mg, of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

One preferred route of administration is inhalation. The major advantages of inhaled medications are their direct delivery to the area of rich blood supply in comparison to many medications taken by oral route. Thus, the absorption is very rapid as the alveoli have an enormous surface area and rich blood supply and first pass metabolism is bypassed.

Preferred pharmaceutical compositions of the invention therefore include those suitable for inhalation. The present invention also provides an inhalation device containing such a pharmaceutical composition. Typically said device is a metered dose inhaler (MDI), which contains a pharmaceutically acceptable chemical propellant to push the medication out of the inhaler. Typically, said propellant is a fluorocarbon.

Further preferred inhalation devices include nebulizers. Nebulizers are devices capable of delivering fine liquid mists of medication through a "mask" that fits over the nose and mouth, using air or oxygen under pressure. They are frequently used to treat those with asthma who cannot use an inhaler, including infants, young children and acutely ill patients of all ages.

Said inhalation device can also be, for example, a rotary inhaler or a dry powder inhaler, capable of delivering a compound of the invention without a propellant.

Typically, said inhalation device contains a spacer. A spacer is a device which enables individuals to inhale a greater amount of medication directly into the lower airways, where it is intended to go, rather than into the throat. Many spacers fit on the end of an inhaler; for some, the canister of medication fits into the device. Spacers with withholding chambers and one-way valves prevent medication from escaping into the air. Many people, especially young children and the elderly, may have difficulties coordinating their inhalation with the action necessary to trigger a puff from a metered dose inhaler. For these patients, use of a spacer is particularly recommended.

Another preferred route of administration is intranasal administration. The nasal cavity's highly permeable tissue is very receptive to medication and absorbs it quickly and efficiently, more so than drugs in tablet form. Nasal drug delivery is less painful and invasive than injections, generating less anxiety among patients. Drugs can be delivered nasally in smaller doses than medication delivered in tablet form. By this method absorption is very rapid and first pass metabolism is bypassed, thus reducing inter-patient variability. Nasal delivery devices further allow medication to be administered in precise, metered doses. Thus, the pharmaceutical compositions of the invention are typically suitable for intranasal administration. Further, the present

invention also provides an intranasal device containing such a pharmaceutical composition.

A further preferred route of administration is transdermal administration. The present invention therefore also provides a transdermal patch containing a compound of the invention, or a pharmaceutically acceptable salt thereof. Also preferred is sublingual administration. The present invention therefore also provides a sub-lingual tablet comprising a compound of the invention or a pharmaceutically acceptable salt thereof.

A compound of the invention is typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose, saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

The compounds of the present invention are therapeutically useful in the treatment or prophylaxis of conditions involving sodium ion flux through a sensory neurone specific (SNS) channel of a sensory neurone. Said condition may be one of hypersensitivity for example resulting from a concentration of SNS channels at the site of nerve injury or in axons following nerve injury, or may be sensitisation of the neurone for example at sites of inflammation as a result of inflammatory mediators.

Said compounds of the invention are therefore most preferred for their use in the treatment or prophylaxis of any condition involving hypersensitivity or sensitisation of a sensory neurone specific (SNS) channel of a sensory neurone.

Accordingly, the present invention also provides the use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment or prophylaxis of a condition involving sodium ion flux through a sensory neurone specific (SNS) channel of a sensory neurone, more specifically hypersensitivity of a sensory neurone or sensitisation of a sensory neurone specific (SNS) channel of a sensory neurone. Also provided is a method of treating a patient suffering from or susceptible to a condition involving sodium ion flux through a sensory neurone specific (SNS) channel of a sensory neurone, more specifically hypersensitivity of a sensory neurone or sensitisation of a sensory neurone specific (SNS) channel of a sensory neurone, which method comprises administering to said patient an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

The term treatment in this context is deemed to cover any effect from a cure of said condition to alleviation of any or all of the symptoms. The compounds of the invention may, where appropriate, be used prophylactically to reduce the incidence or severity of said conditions.

Specific conditions in which SNS channels are present and believed to be involved include pain, for example chronic and acute pain, hypersensitivity disorders such as bladder dysfunction and bowel disorders which may or may not also have associated pain, and demyelinating diseases.

SNS sodium channels are known to mediate pain transmission. Typically, the compounds of the invention are therefore used as analgesic agents. SNS specific sodium channels have been identified as being particularly important in the transmission of pain signals. The compounds of the invention are accordingly

particularly effective in alleviating pain. Typically, therefore, said medicament is for use in alleviating pain and said patient is suffering from or susceptible to pain. The compounds of the invention are effective in alleviating both chronic and acute pain.

Acute pain is generally understood to be a constellation of unpleasant sensory, perceptual and emotional experiences of certain associate autonomic (reflex) responses, and of psychological and behavioural reactions provoked by injury or disease. A discussion of acute pain can be found at Halpern (1984) *Advances in Pain Research and Therapy,* Vol.7, p.147. Tissue injury provokes a series of noxious stimuli which are transduced by nociceptors to impulses transmitted to the spinal cord and then to the upper part of the nervous system. Examples of acute pains which can be alleviated with the compounds of the invention include musculoskeletal pain, for example joint pain, lower back pain and neck pain, dental pain, post-operative pain, obstetric pain, for example labour pain, acute headache, neuralgia, myalgia, and visceral pain.

Chronic pain is generally understood to be pain that persists beyond the usual course of an acute disease or beyond a reasonable time for an injury to heal. A discussion of chronic pain can be found in the Halpern reference given above. Chronic pain is sometimes a result of persistent dysfunction of the nociceptive pain system. Examples of chronic pains which can be alleviated with the compounds of the invention include trigeminal neuralgia, post-herpetic neuralgia (a form of chronic pain accompanied by skin changes in a dermatomal distribution following damage by acute Herpes Zoster disease), diabetic neuropathy, causalgia, “phantom limb” pain, pain associated with osteoarthritis, pain associated with rheumatoid arthritis, pain associated with cancer, pain associated with HIV, neuropathic pain, migraine and other conditions associated with chronic cephalic pain, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, spinal cord injury pain, central pain, post-herpetic pain, noncardiac chest pain, irritable bowel syndrome and pain associated with bowel disorders and dyspepsia.

Some of the chronic pains set out above, for example, trigeminal neuralgia, diabetic neuropathic pain, causalgia, phantom limb pain and central post-stroke pain, have also been classified as neurogenic pain. One non-limiting definition of neurogenic pain is pain caused by dysfunction of the peripheral or central nervous system in the absence of nociceptor stimulation by trauma or disease. The compounds of the invention can, of course, be used to alleviate or reduce the incidence of neurogenic pain

Examples of bowel disorders which can be treated or prevented with the compounds of the invention include inflammatory bowel syndrome and inflammatory bowel disease, for example Crohn's disease and ulcerative colitis.

Examples of bladder dysfunctions which can be treated or prevented with the compounds of the invention include bladder hyper reflexia and bladder inflammation, for example interstitial cystitis. The compounds of the invention can also be used to alleviate pain associated with bladder hyper reflexia or bladder inflammation.

Examples of demyelinating diseases which can be treated or prevented with the compounds of the invention are those in which SNS channels are known to be expressed by the demyelinated neurones and which may or may not also have associated pain. A specific example of such a demyelinating disease is multiple sclerosis. The compounds of the invention can also be used to alleviate pain associated with demyelinating diseases such as multiple sclerosis.

The compounds of the invention have additional properties as they are capable of inhibiting voltage dependent sodium channels. They can therefore be used, for example, to protect cells against damage or disorders which results from overstimulation of sodium channels.

The compounds of the invention and can additionally be used in the treatment or prevention of an affective disorder, an anxiety disorder, a behavioural disorder, a cardiovascular disorder, a central or peripheral nervous system degenerative disorder, a central nervous system injury, a cerebral ischaemia, a chemical injury or substance abuse disorder, a cognitive disorder, an eating disorder, an eye disease, Parkinson's disease or a seizure disorder.

Examples of affective disorders which can be treated or prevented with the compounds of the invention include mood disorders, bipolar disorders (both Type 1 and Type II) such as seasonal affective disorder, depression, manic depression, atypical depression and monodepressive disease, schizophrenia, psychotic disorders, mania and paranoia.

Examples of anxiety disorders which can be treated or prevented with the compounds of the invention include generalised anxiety disorder (GAD), panic disorder, panic disorder with agoraphobia, simple (specific) phobias (e. g. arachnophobia, performance anxiety such as public speaking), social phobias, post-traumatic stress disorder, anxiety associated with depression, and obsessive

compulsive disorder (OCD).

Examples of behavioural disorders which can be treated or prevented with the compounds of the invention include behavioural and psychological signs and symptoms of dementia, age-related behavioural disorders, pervasive development disorders such as autism, Asperger's Syndrome, Retts syndrome and disintegrative disorder, attention deficit disorder, aggressivity, impulse control disorders and personality disorder.

Examples of cardiovascular disorders which can be treated or prevented with the compounds of the invention include cardiac arrthymia, atherosclerosis, cardiac arrest, thrombosis, complications arising from coronary artery bypass surgery, myocardial infarction, reperfusion injury, intermittant claudication, ischaemic retinopathy, angina, pre-eclampsia, hypertension, congestive cardiac failure, restenosis following angioplasty, sepsis and septic shock.

Examples of central and peripheral nervous system degenerative disorders which can be treated or prevented with the compounds of the invention include corticobasal degeneration, disseminated sclerosis, Freidrich's ataxia, motorneurone diseases such as amyotrophic lateral sclerosis and progressive bulbar atrophy, multiple system atrophy, myelopathy, radiculopathy, peripheral neuropathies such as diabetic neuropathy, tabes dorsalis, drug-induced neuropathy and vitamin deficiency, systemic lupus erythamatosis, granulomatous disease, olivo-ponto-cerebellar atrophy, progressive pallidal atrophy, progressive supranuclear palsy and spasticity.

Examples of central nervous system injuries which can be treated with the compounds of the invention include traumatic brain injury, neurosurgery (surgical trauma), neuroprotection for head injuries, raised intracranial pressure, cerebral oedema, hydrocephalus and spinal cord injury.

Examples of cerebral ischaemias which can be treated or prevented with the compounds of the invention include transient ischaemic attack, stroke, for example thrombotic stroke, ischaemic stroke, embolic stroke, haemorrhagic stroke or lacunar stroke, subarachnoid haemorrhage, cerebral vasospasm, peri-natal asphyxia, drowning, cardiac arrest and subdural haematoma.

Examples of chemical injuries and substance abuse disorders which can be treated or prevented with the compounds of the invention include drug dependence, for example opiate dependence, benzodiazepine addition, amphetamine addiction

and cocaine addiction, alcohol dependence, methanol toxicity, carbon monoxide poisoning and butane inhalation.

Examples of cognitive disorders which can be treated or prevented with the compounds of the invention include dementia, Alzheimer Disease, Frontotemporal dementia, multi-infarct dementia, AIDS dementia, dementia associated with Huntingtons Disease, Lewy body Dementia, Senile dementia, age-related memory impairment, cognitive impairment associated with dementia, Korsakoff syndrome and dementia pugilans.

Examples of eating disorders which can be treated or prevented with the compounds of the invention include anorexia nervosa, bulimia, Prader-Willi syndrome and obesity.

Examples of eye diseases which can be treated or prevented with the compounds of the invention include drug-induced optic neuritis, cataract, diabetic neuropathy, ischaemic retinopathy, retinal haemorrhage, retinitis pigmentosa, acute glaucoma, in particular acute normal tension glaucoma, chronic glaucoma, in particular chronic normal tension glaucoma, macular degeneration, retinal artery occlusion and retinitis.

Examples of Parkinson's diseases which can be treated or prevented with the compounds of the invention include drug-induced Parkinsonism, post-encephalitic Parkinsonism, Parkinsonism induced by poisoning (for example MPTP, manganese or carbon monoxide poisoning), Dopa-responsive dystonia-Parkinsonism, posttraumatic Parkinson's disease (punch-drunk syndrome), Parkinson's with on-off syndrome, Parkinson's with freezing (end of dose deterioration) and Parkinson's with prominent dyskinesias.

Examples of seizure disorders which can be treated or prevented with the compounds of the invention include epilepsy and post-traumatic epilepsy, partial epilepsy (simple partial seizures, complex partial seizures, and partial seizures secondarily generalised seizures), generalised seizures, including generalised tonicclonic seizures (grand mal), absence seizures (petit mal), myoclonic seizures, atonic seizures, clonic seizures, and tonic seizures, Lennox Gastaut, West Syndome (infantile spasms), multiresistant seizures and seizure prophylaxis (antiepileptogenic).

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, for example 0.01 to 10 mg, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

The following Examples illustrate the invention. They do not, however, limit the invention in any way. In this regard, it is important to understand that the particular assays used in the Examples section are designed only to provide an indication of activity in inhibiting SNS specific sodium channels. A negative result in any one particular assay is not determinative.

EXAMPLES

Example 1: N-Benzhydryl-2-chloro-acetamide

To a stirred solution of aminodiphenylmethane (Aldrich A5,360-5) (4.36g, 25.3 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (Aldrich 47,128-3) (2.81g, 27.77 mmol). The reaction mixture was cooled to approximately 10°C and chloroacetylchloride (Aldrich 10,449-3) (3.14g, 27.83 mmol) was added drop-wise over 5 min. The reaction mixture was stirred for 2h and quenched by the addition of distilled H_2O (50 mL). The layers were separated and the organic layer washed with brine (50 mL), dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford the *title compound*as a white solid (0.78g, 12%): HPLC retention time 3.67min ((Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6 min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5 mL/min.). Mass Spectrum (ES+) m/z 260 (M+H).

The following compounds were synthesized from the appropriate diphenylalkylamine and chloroacetylchloride according to the method described above:

2-Chloro-N-(2,2-diphenyl-ethyl)-acetamide;
2-Chloro-N-(3,3-diphenyl-propyl)-acetamide;
N-Benzyl-2-chloro-N-phenyl-acetamide;
N,N-Dibenzyl-2-chloro-acetamide;
2-Chloro-N-(9H-flurenyl-9-yl)-acetamide;
N,N-Dibenzyl-3-chloro-propionamide;
2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone; and
2-Chloro-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone.

Example 2: 2-Chloro-N-(4,4-diphenyl-butyl)-acetamide

To a stirred solution of 1-Bromo-3,3-diphenylpropane (Acros 27191231) (2g, 7.27mmol) in dimethyl sulphoxide (5 mL) was added potassium cyanide (Aldrich 20,781-0) (0.57g, 8.73mmol). The reaction mixture was stirred at room temperature

for 19h and quenched by the addition of distilled H_2O (20 mL). The resulting solution was extracted with EtOAc (3 x 20 mL) the combined organic layers dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The resulting residue was dissolved in anhydrous tetrahydrofuran (25 mL) and borane-tetrahydrofuran complex (Aldrich 17,619-2) (1M, 27 mL, 27mmol) was added drop wise over 5min. The reaction mixture was heated at reflux for 2h, cooled to 0°C and quenched with CH_3OH (10 mL). The solvent was removed *in vacuo* and the residue azeotroped with CH_3OH (3 x 15 mL).The residue was dissolved in CH_2Cl_2 (20 mL) and Et_3N (1.39g, 13.69mmol) was added. The reaction mixture was cooled to approximately 10°C and chloroacetylchloride (Aldrich 10,449-3) (1.55g, 12.44mmol) was added drop-wise over 5min. The reaction mixture was stirred for 4h and quenched with distilled H_2O (20 mL). The organic layer was separated, dried ($MgSO_4$) and the solvent removed *in vacuo* .The residue was purified by flash column chromatography to afford the *title compound*as a viscous oil (1.8g, 85%) : HPLC retention time 4.04min ((Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 302 (M+H).

Example 3: 3-Chloro-N-(3,3-diphenyl-propyl)-propionamide

To a stirred solution of 3,3 Diphenylpropylamine (Acros 15948-0250) (6.5g, 30.7mmol) in CH_2Cl_2 (50 mL) was added Et_3N (Aldrich 47,128-3) (2.81g, 27.77 mmol). The reaction mixture was cooled to approximately 10°C and 3-chloropropionyl chloride (Aldrich C6,912-8) (4.29g, 30.7mmol) was added drop-wise over 5 min. The reaction mixture was stirred for 2h and quenched by the addition of distilled H_2O (50 mL). The layers were separated and the organic layer washed with brine (50 mL), dried (Na_2SO_4) and the solvent remove *in vacuo* . The residue was purified by flash column chromatography and recrystallisation from EtOAc to afford the *title compound*as a white solid (3.1g, 33%): HPLC retention time 3.98min ((Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 302 (M+H).

Example 4: 8-Methoxyisoquinoline

Ref: Y. Yoshida et al Bioorg. Med. Chem. 7 (1999) 2647-2666.

To a 1 L round bottom flask, equipped with a Dean-Stark trap, was added 2-methoxybenzaldehyde (Aldrich 10,962-2) (23.8g, 175mmol) in benzene (850 mL). To this stirred solution was added 2,2-dimethoxyethylamine (Aldrich 12,196-7) (18.3g, 175 mmol). The reaction mixture was refluxed for 5h, cooled to room temperature and the solvent removed in vacuo. The residue was dissolved in tetrahydrofuran (238 mL) and cooled to c.a.-10°C, (external temperature maintained between -8°C to -10°C with acetone/card-ice). To this cooled solution was added ethyl chloroformate (Aldrich 18,589-2) (18.9g, 174 mmol) over c.a, 5 min. The reaction mixture was allowed to warm to room temperature and treated with trimethyl phosphite (Aldrich T7,970-7) (25 mL, 212 mmol). The reaction mixture was stirred at room temperature for 60h, and evaporated *in vacuo* to give an oil. This oil was dissolved in CH_2Cl_2 (238 mL) and cooled to 0°c (external temperature), treated with titanium tetrachloride (Aldrich 20,856-6) (200 g, 1.0 mol) over c.a. 8min, warmed to room temperature, heated at reflux for 3h, cooled to room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (800mL) and cooled to c.a. 0°C and basified with 30% sodium hydroxide solution. The neutralised mixture was filtered through celite/sand diluting with c.a. 5 L of CH_2Cl_2. The CH_2Cl_2 layer was separated and dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting brown oil is purified by flash column chromatography using CH_2Cl_2/CH_3OH, 90/10, v/v as mobile phase to give the *title compound*as a red oil (19.7 g, 70%). ^{1}H NMR (400MHz, DMSO-d_6) δ 4.02 (3H), 7.12 (1H), 7.55 (1H), 7.75 (1H,), 7.8 (1H), 8.50 (1H), 9.55 (1H).

Example 5: Isoquinolin-8-ol

Ref: Y. Yoshida et al Bioorg. Med. Chem. 7 (1999) 2647-2666.

To a stirred solution of 8-methoxyisoquinoline (7.0g, 44mmol) in anhydrous CH_2Cl_2 (60 mL) cooled in an ice bath, was added over 0.5h, boron tribromide, 1M in CH_2Cl_2

(Aldrich 21,122-2) (219 mL, 219 mmol). The reaction mixture was warmed to room temperature, heated at reflux for 2h, cooled to -78°C, and decomposed by the addition of CH_3OH (150 mL). The reaction mixture was warmed to room temperature, heated at reflux for 0.5h and the solvent removed *in vacuo*. The residue was azeotroped with CH_3OH (3 x 100 mL) and suspended in H_2O (150 mL). To this suspension was added CH_2Cl_2 (300 mL) and with vigorous stirring neutralised to c.a. 7.0 with ammonia (0.88). The CH_2Cl_2 layer was separated and the aqueous layer extracted with CH_2Cl_2 (2 x 200 mL). The combined layers were dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was purified by flash column chromatography to give the *title compound*as a pale yellow solid. (6.87g, 98%). ^1H NMR (400MHz, DMSO-d_6) δ 7.10 (1H), 7.45 (1H), 7.65 (1H,), 7.75(1H), 8.50 (1H), 9.50 (1H), 10.90 (1H).

Example 6: 1,2,3,4-Tetrahydro-isoquinolin-8-ol acetate salt

US Patent 3,575,983

To a stirred solution of Isoquinolin-8-ol (2.0g, 13.8mmol) in ethanol (120 mL) was added acetic acid (2 mL) and platinium (IV) oxide (Aldrich 45,992-5) (0.2g). The reaction mixture was hydrogenated at c.a. 4bar for 18h. The catalyst was filtered off and the solvent removed *in vacuo* to give the *title compound*as a tan solid (5.2g, 92%) : HPLC retention time 2.0min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.).
Mass Spectrum (ES+) m/z 150 (M+H).

Example 7: 8-Methoxy-1,2,3,4-tetrahydro-isoquinoline acetate salt

8-Methoxy-1,2,3,4-tetrahydro-isoquinoline acetate salt was prepared from 8-Methoxyisoquinoline and platinium (IV) oxide (Aldrich 45,992-5) according to the method described in Example 6 : HPLC retention time 3.33min (Solvent: MeCN/

H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.) : Mass Spectrum (ES+) m/z 164 (M+H).

Example 8: 2-(2-Dibenzylamino-ethyl)1,2,3,4-tetrahydro-isoquinolin-8-ol)

To a stirred suspension of 1,2,3,4-Tetrahydro-isoquinolin-8-ol acetate salt (1.0g, 4.78mmol) in MeCN (50mL) was added N-(chloroethy)dibenzylamine hydrochloride (Aldrich 29,136-6) (1.42g, 4.78mmol), tetrabutlylammonium iodide (Aldrich 14,077-5) (0.29g, 0.79mmol) and potassium carbonate (Acros) (0.66g, 4.78mmol). The reaction mixture was heated at 95°C for 7h and cooled to room temperature, filtered and the solvent removed *in vacuo* .The residue was dissolved in CH_2Cl_2 (80mL), washed with H_2O (25mL), dried (Na_2SO_4) and the solvent remove *in vacuo* . The residue was purified by flash column chromatography using CH_2Cl_2/CH_3OH/ ammonia, 95/5/0.2, v/v/v, as mobile phase to give the *title compound*as a low melting solid (0.71g, 39%) : 1H NMR (400MHz, CDCl3) δ_H 2.6-2.9 (8H), 3.55 (2H), 3.65(4H), 6.5(1H), 6.95(1H), 7.2-7.5(11H). HPLC retention time 7.27min ((Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 373 (M+H).

Example 9 : 2-[4,4-Bis-(4-fluro-phenyl)-butyl]-1,2,3,4-tetrahydro-isoquinoline

2-[4,4-Bis-(4-fluro-phenyl)-butyl]-1,2,3,4-tetrahydro-isoquinoline was prepared from 1,2,3,4-tetrahydroisoquinoline(AldrichA5,5560-8) and 1-1'-(4-chloro-butylidene)-bis-(flurobenzene), (Acros 123390) according to the method described in Example 8: HPLC retention time 8.29min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 378(M+H).

Example 10: 2-[4,4-Bis-(4-fluro-phenyl)-butyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline

2-[4,4-Bis-(4-fluro-phenyl)-butyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline was prepared from 8-methoxy-1,2,3,4-tetrahydroisoquinoline) and 1-1'-(4-chloro-butylidene)-bis-(flurobenzene) (Acros 123390) according to the method described in Example 8 : HPLC retention time 8.39min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 408(M+H).

Example 11: 2-(2,2-Diphenyl-ethyl)-1,2,3,4-tetrahydro-isoquinoline-8-ol

To a stirred solution of 1,2,3,4-Tetrahydro-isoquinolin-8-ol acetate salt (0.120g, 0,57mmol) in CH_3OH (5mL) was added Et_3N (Aldrich 47,128-3) (0.058g, 0.57mmol). The reaction mixture was stirred for 0.5h , diphenylacetaldehyde (Aldrich D20-245-0) (0.113g, 0.57mmol) in CH_3OH (5mL), and sodium cyanoborohydride (Aldrich15,615-9) (0.036g, 0.57mmol) was added. The reaction mixture was stirred for 18h. The solvent was removed in vacuo and the residue was purified by flash column chromatography using CH_2Cl_2/CH_3OH, 95/5 vv/ to afford the *title compound*as a white solid (0.032g, 17%) : HPLC retention time 3.21min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 330(M+H).

Example 12: 2-(2,2-Diphenyl-ethyl)1,2,3,4-tetrahydro-isoquinoline

2-(2,2-Diphenyl-ethyl)1,2,3,4-tetrahydro-isoquinoline was prepared from 1,2,3,4-tetrahydroisoquinoline (AldrichA5,5560-8) and diphenylacetaldehyde (Aldrich D20-245-0) according to the method described in Example 11 with the following modification: CH_2Cl_2 was used as the reaction solvent: HPLC retention time 4.96min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 314(M+H).

Example 13: 2-(2,2-Diphenyl-ethyl)-8-methoxy-1,2,3,4-tetrahydro-isoquinoline

2,2-Diphenyl-ethyl)-8-methoxy-1,2,3,4-tetrahydro-isoquinoline was prepared from 8-methoxy-1,2,3,4-tetrahydroisoquinoline(AldrichA5,5560-8) and diphenylacetaldehyde (Aldrich D20-245-0) according to the method described in Example 11 with the following modification: CH_2Cl_2 was used as the reaction solvent : HPLC retention time 4.96min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 344(M+H).

Example 14: N-Benzyhydryl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

To a stirred solution of 1,2,3,4-Tetrahydroisoquinoline (AldrichA5,5560-8) (0.133g, 1mmol) in MeCN (15mL) was added potassium carbonate (Acros P/4120/50) 0.138g, 1mmol)), tetrabutlylammonium iodide (Aldrich 14,077-5) (0.074g, 0.02mmol). To this suspension was added N-Benzhydryl-2-chloro-acetamide (0.259g, 1mmol) in MeCN (10mL). The reaction mixture was heated at reflux for 8h, cooled to room temperature and filtered. The solvent was removed in vacuo and the residue purified by flash column chromatography using iso-hexane.EtOAc as mobile phase to afford the *title compound*as a clear oil (0.256g, 72%) : HPLC retention time 4.26min (Solvent: MeCN/H2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 357(M+H).

Example 15: 2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-(9H-fluorenyl)-acetamide

2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-(9H-fluorenyl)-acetamide was prepared from 1,2,3,4-tetrahydroisoquinoline (AldrichA5,5560-8) and 2-Chloro-N-(9H-flurenyl-9-yl)-acetamide according to the method described in Example 14 : HPLC retention time 4.34min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 355(M+H).

Example 16: N,N-Dibenzyl-2-(3,4-dihydro-1H-isoquinolin-2yl)-acetamide

N,N-Dibenzyl-2-(3,4-dihydro-1H-isoquinolin-2yl)-acetamide was prepared from 1,2,3,4-tetrahydroisoquinoline (AldrichA5,5560-8) and N,N-Dibenzyl-2-chloro-acetamide according to the method described in Example 14: HPLC retention time 4.41min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 371(M+H).

Example 17: N-Benzyl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide

N-Benzyl-2-(3,4-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide was prepared from 1,2,3,4-tetrahydroisoquinoline (AldrichA5,5560-8) and N,N-Dibenzyl-3-chloro-propionamide according to the method described in Example 14 : HPLC retention time 4.24min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 357(M+H).

Example 18: 2-(3,4-Dihydro-1H-isoquinolin-2yl)-N-(3,3-diphenyl-propyl)-acetamide

2-(3,4-Dihydro-1H-isoquinolin-2yl)-N-(3,3-diphenyl-propyl)-acetamide was prepared from 1,2,3,4-tetrahydroisoquinoline (AldrichA5,5560-8) and 2-Chloro-N-(3,3-diphenyl-propyl)-acetamide according to the method described in Example 14 : HPLC retention time 4.35min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 385(M+H).

Example 19: N-Benzylhydryl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-Benzylhydryl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-methoxy-1,2,3,4-tetrahydroisoquinoline and N-Benzhydryl-2-chloro-acetamide according to the method described in Example 14 : HPLC retention time 4.30min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min.

Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 387(M+H).

Example 20: N-(9H-Fluorenyl-9-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-acetamide

N-(9H-Fluorenyl-9-yl)-20(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-acetamide was prepared from 8-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-Chloro-N-(9H-flurenyl-9-yl)-acetamide according to the method described in Example 14 : HPLC retention time 4.20min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 385(M+H).

Example 21: N-Benzylhydryl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide

N-Benzylhydryl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide was prepared from 8-methoxy-1,2,3,4-tetrahydroisoquinoline and N,N-Dibenzyl-3-chloro-propionamide according to the method described in Example 14. HPLC retention time 4.15min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 387(M+H).

Example 22: N-(3,3-Diphenyl-propyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(3,3-Diphenyl-propyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-methoxy-1,2,3,4-tetrahydroisoquinoline and 2-Chloro-N-(3,3-diphenyl-propyl)-acetamide according to the method described in Example 14 : HPLC retention time 4.22min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 415(M+H).

Example 23: N,N-Dibenzyl-2-(8-hydroxy-3,3-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-Dibenzyl-2-(8-hydroxy-3,3-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-hydroxy-1,2,3,4-tetrahydroisoquinoline and N,N-Dibenzyl-2-chloro-acetamide according to the method described in Example 14 : HPLC retention time 4.21min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 387(M+H).

Example 24: N-Benzylhydryl-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-Benzylhydryl-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-hydroxy-1,2,3,4-tetrahydroisoquinoline and N-Benzhydryl-2-chloro-acetamide according to the method described in Example 14 : HPLC retention time 4.03min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 373(M+H).

Example 25: N,-Benzyl-2-(8-hydroxy-3,3-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide

N,-Benzyl-2-(8-hydroxy-3,3-dihydro-1H-isoquinolin-2-yl)-N-phenyl-acetamide was prepared from 8-hydroxy-1,2,3,4-tetrahydroisoquinoline N,N-Dibenzyl-3-chloro-propionamide according to the method described in Example 14 : HPLC retention time 3.99min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 373(M+H).

Example 26: N-(9H-fluoren-9-yl)-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,-(9H-fluoren-9-yl)-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-hydroxy-1,2,3,4-tetrahydroisoquinoline and 2-Chloro-N-(9H-flurenyl-9-yl)-acetamide according to the method described in Example 14 : HPLC retention time 4.02min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 371(M+H).

Example 27: N-(3,3-Diphenyl-propyl)-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(3,3-Diphenyl-propyl)-2-(8-hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-hydroxy-1,2,3,4-tetrahydroisoquinoline and 2-Chloro-N-(3,3-diphenyl-propyl)-acetamide according to the method described in Example 14 : HPLC retention time 4.10min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 401(M+H).

Example 28: 2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-[1-(5-methyl-thiazol-2-yl)-ethyl]-acetamide

2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-[1-(5-methyl-thiazol-2-yl)-ethyl]-acetamide was prepared from 1,2,3,4-tetrahydroisoquinoline(AldrichA5,5560-8) and 2-chloro-N-[1-methyl-thiazol-2-yl)-ethyl]- acetamide according to the method described in Example 14 HPLC retention time 3.73min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 316(M+H).

Example 29: 2-(8-Hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-[1-(5-methyl-thiazol-2-yl)-ethyl]-acetamide

2-(8-Hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-[1-(5-methyl-thiazol-2-yl)-ethyl]-acetamide was prepared from 8-Hydroxy-1,2,3,4-tetrahydroisoquinoline (AldrichA5,5560-8) and 2-chloro-N-[1-methyl-thiazol-2-yl)-ethyl]- acetamide according to the method described in Example 14 : HPLC retention time 3.21min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 332(M+H).

Example 30: 1-(3,4-Dihydro-1H-isoquinoline-2-yl-3,3-bis-(4-fluoro-phenyl)-propan-1-one

To a stirred solution of 1,2,3,4-Tetrahydroisoquinoline (AldrichA5,5560-8) (0.102g, 0.76mmol) in CH_2Cl_2 (5mL) was added 3,3-Bis-(4-fluro-phenyl)-propionyl chloride (0.107g, 0.33mmol). The reaction mixture was stirred for 5h and the solvent removed in vacuo. The residue was purified by flash column chromatography using CH_2Cl_2as mobile phase followed by preparative HPLC (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.), to give the *title compound*as an oil (3.4mgs, (2%) : HPLC retention time 4.39min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 378(M+H).

Example 31: 2-(Benzhydryl-amino)-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

To a stirred solution of 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone (0.150g, 0..71mmol) in acetonitril was added of aminodiphenylmethane (Aldrich A5,360-5) (0.131g, 0.71mmol), tetrabutlylammonium iodide (Aldrich 14,077-5) (0.53g, 0.14mmol) and potassium carbonate (Acros) (0.99g, 0.71mmol). The reaction mixture was heated at reflux for 5h and cooled to room temperature and the

solvent removed in vacuo. The residue was purified by column chromatography using EtOAc/iso-hexane, 1/1, v/v, to give the *title compound*as a colourless oil (0.10g, 39%) : HPLC retention time 6.65min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 357(M+H).

Example 32: 1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(2,2-diphenyl-ethylamino)-ethanone

To a stirred solution of 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone (0.209g, 0..1.0mmol) in was added (0.197g, 1.0mmol), 2,2-Diphenylpropyamine (Aldrich D20-670-9)(0.2113g, 1.0mmol) tetrabutlylammonium iodide (Aldrich 14,077-5) (0.369g, 0.074mmol) and potassium carbonate (Acros) (0.99g, 0.71mmol). The reaction mixture was heated at reflux for 18h, cooled to room temperature and the solvent removed in vacuo. The residue was purified by column chromatography using EtOAc/iso-hexane, 1/3, v/v, to give the *title compound*as a colourless oil (0.047g,12 %) : HPLC retention time 4.24min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 385(M+H).

Example 33: 1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-[[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-(3,3-diphenyl-propyl)-amino]-ethanone

1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-[[2-(3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-(3,3-diphenyl-propyl)-amino]-ethanone was prepared from 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone and 2,2-Diphenylpropyamine (Aldrich D20-670-9) according to the method described in Example 31 : HPLC retention time 4.7min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.) : HPLC retention time 4.70min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 558(M+H).

Example 34: 1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(3,3-diphenyl-propylamino)-ethanone

1-(3,4-Dihydro-1H-isoquinolin-2-yl)-2-(3,3-diphenyl-propylamino)-ethanone was prepared from 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone and 3,3-Diphenylpropylamine (Acros 15948-0250) according to the method described in Example 31 : HPLC retention time 4.30min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 385(M+H).

Example 35: 2-Dibenzylamino-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2-Dibenzylamino-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone and N-Phenyl benzylamine (Aldrich 18549-3) according to the method described in Example 31 : HPLC retention time 4.72min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 371(M+H).

Example 36: 2-{(2,2-Diphenyl-ethyl)-[2-8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-amino}-1H-isoquinolin-2yl)-ethanone

2-{(2,2-Diphenyl-ethyl)-[2-8-methoxy-3,4-dihydro-IH-isoquinolin-2-yl)-2-oxo-ethyl]-amino}-1H-isoquinolin-2yl)-ethanone was prepared from 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone and 2,2-Diphenylpropyamine (Aldrich D20-670-9) according to the method described in Example 31 : HPLC retention time 4.75min (Solvent: $MeCN/H_2O/0.05\%\ HCOOH$, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 604(M+H).

Example 37: 2-{Benzhydryl-[2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-2-oxo-ethyl]-amino}-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2-{Benzhydryl-[2-(8-methoxy-3,4-dihydro-!H-isoquinolin-2-yl)-2-oxo-ethyl]-amino}-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 2-Chloro-1-(8-methoxy-3,4-dihydro-1H-isoquinoline 2-yl)-ethanone and aminodiphenylmethane (Aldrich A5,360-5) according to the method described in Example 31 : HPLC retention time 7.57min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 560(M+H).

Example 38: 2-(Benzhydryl-amino)-1-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethanone

2-(Benzhydryl-amino)-1-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethanone was prepared from 2-Chloro-1-(8-methoxy-3,4-dihydro-1H-isoquinoline 2-yl)-ethanone and aminodiphenylmethane (Aldrich A5,360-5) according to the method described in Example 31 : HPLC retention time 6.18min (Solvent: MeCN/ H_2O/ 0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 387(M+H).

Example 39: 2-(2,2-Diphenyl-ethylamino)-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

2-(2,2-Diphenyl-ethylamino)-1-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone and 2,2-Diphenylpropyamine (Aldrich D20-670-9) according to the method described in Example 31 : HPLC retention time 6.65min (Solvent: MeCN/H_2O/ 0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 401(M+H).

Example 40: 2-(1,3-Dihydro-isoindol-2-yl)-N-(3,3-diphenyl-propyl)-acetamide

To a stirred solution of isoindoline (Aldrich 51,557-4) (0.25g, 2.1mmol) in MeCN (15mL) was added 2-Chloro-N-(3,3-diphenyl-propyl)-acetamide (0.60g, 2.1mmol), tetrabutlylammonium iodide (Aldrich 14,077-5) (0.16g, 0.42mmol) and Et_3N) (Aldrich 47,128-3) (600µl, 2.1mmol). The reaction mixture was heated at reflux for 4h and cooled to room temperature, and the solvent removed *in vacuo* .The residue was dissolved in CH_2Cl_2 (100mL), washed with H_2O (20mL), dried (Na_2SO_4) and the solvent remove *in vacuo* . The residue was purified by flash column chromatography using EtOAc/iso-hexane, 1/1 as mobile phase to give the *title compound*as a tan solid (0.25g, 32%) : HPLC retention time 4.33min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 371(M+H).

Example 41: N-Benzhydryl-2-(1,3-dihydro-isoindol-2-yl)-acetamide

N-Benzhydryl-2-(1,3-dihydro-isoindol-2-yl)-acetamide was prepared from isoindoline (Aldrich 51,557-4) and aminodiphenylmethane (Aldrich A5,360-5) according to the method described in Example 40 : HPLC retention time 4.32min (Solvent: MeCN/H_2O/0.05% NH_3; 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 343(M+H).

Example 42: 2-Benzhydrylideneaminooxy-1-(3,4-dihydro-1H-isoquinoline-2-yl)-ethanone

To a suspension of sodium hydride 60% dispersion in mineral oil (Aldrich 2,344-1) in dimethyl foramide (2mL) cooled in an ice bath was added benzophenone oxime (Lancaster 0817) (0.47g, 2.39mmol). The reaction mixture was removed from the ice bath and stirred at room temperature for 0.5h. To this solution was added 2-Chloro-1-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone (0.5g, 2.39mmol) in dimethyl formamide (1mL). The reaction was stirred for 18h, diluted with H_2O (30mL),

extracted with Et_2O (50mL), dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by preparative HPLC (Solvent: $MeCN/H_2O$/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 15mL/min.) to give the *title compound*as a glass (0.44g, 55%) : HPLC retention time 4.53min (Solvent: $MeCN/H_2O$/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 371(M+H).

Example 43: 2-Benzhydrylideneaminooxy-1-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethanone

2-Benzhydrylideneaminooxy-1-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethanone was prepared from benzophenone oxime (Lancaster 0817) and 2-Chloro-1-(8-methoxy-3,4-dihydro-1H-isoquinoline 2-yl)-ethanone according to the method described in Example 42 : HPLC retention time 4.48min (Solvent: $MeCN/H_2O$/ 0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 401(M+H).

Example 44: 2-(Di-pyridin-2-yl-methyleneaminooxy)-1-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethanone

2-(Di-pyridin-2-yl-methyleneaminooxy)-1-(8-methoxy-3,4-dihydro-1H-isoquinoline-2-yl)-ethanone was prepared from Di-2-pyridyl ketone oxime (Aldrich 16,170-5) and 2-Chloro-1-(8-methoxy-3,4-dihydro-1H-isoquinoline 2-yl)-ethanone according to the method described in Example 42 : HPLC retention time 3.50min (Solvent: MeCN/ H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 403(M+H).

Example 45: 2-(5-Phenyl-2H-[1,2,3]triazol-4-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

5-Phenyl-2H-[1,2,3]-triazole-4-carbaldehyde:

To a stirred solution of phenylacetylene (Aldrich 11,770-6) (5.1g, 50 mmol) in anhydrous tetrahydrofuran (125 mL) at - 40°C under nitrogen was added dropwise over c.a 2 min nButyl lithium (Aldrich 18,617-1) (31.3 mL, 50 mmol) whilst maintaining the temperature (internal) between -35°C to - 40°C with external cooling. To this solution was added anhydrous dimethyl formamide (7.75 mL) and the reaction mixture allowed to warm to room temperature, stirred for 0.5h and quenched by pouring into a rapidly stirred biphasic solution of 10% potassium dihydrogen phosphate (270 mL) and methyl tert-butyl ether (250 mL), cooled to c.a. -5°C. The layers were separated and the aqueous layer back extracted with methyl tert-butyl ether (100 mL). The combined organic layers were washed with H_2O (2 x 200 mL), dried ($MgSO_4$) and evaporated to dryness *in vacuo* to give a yellow oil which was purified by flash column chromatography to give 6.1g of a pale yellow oil. A solution of this oil (3.1g in dimethyl sulphoxide (17.5 mL) was added to a vigorously stirred solution of sodium azide (Aldrich 19,993-1) (1.79g, 27.5 mmol) over c.a. 10 min whilst maintaining the temperature (internal) between 20 to 25°C. The reaction mixture was stirred for a further 0.5h and quenched by pouring into a rapidly stirred biphasic solution of 15% potassium dihydrogen phosphate (150 mL) and methyl tert-butyl ether (160 mL). The organic layer was separated and washed with H_2O (2 x100 mL). The aqueous layers were re-extracted with methyl tert-butyl ether (100 mL) and the combined organic layers dried over ($MgSO_4$) and evaporated *in vacuo* to afford the *title compound*as an off white solid (3.1g, 65%): ^1H NMR (400MHz, $CDCl_3$) δH 7.46-7.59 (3H), 7.66-7.89 (2H), 10.14 (1H), 16.08 (1H,).

2-(5-Phenyl-2H-[1,2,3]triazol-4-ylmethyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol:

To a stirred solution of 1,2,3,4-Tetrahydro-isoquinolin-8-ol acetate salt (0.120g, 0,57mmol) in CH_3OH (5mL) was added Et_3N (Aldrich 47,128-3) (0.058g, 0.57mmol). The reaction mixture was stirred for 0.5h , 5-phenyl-2H-[1,2,3]-triazole-

4-carbaldehyde (0.025g, 0.14mmol) in CH_3OH (5mL), and sodium cyanoborohydride (Aldrich15,615-9) (0.009g, 0.14mmol) was added. The reaction mixture was heated at reflux for 5h, cooled to room temperature and the solvent removed in vacuo . The residue was purified by flash column chromatography using EtOAc/iso-hexane 1/1, v/v as mobile phase to afford the *title compound*as a viscous oil (0.004g, 10%) : HPLC retention time 2.54min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 306(M+H).

Example 46: [2-(3,4-Dihydro-1H-isoquinolin-2-yl)-ethyl]-(3,3-diphenyl-propyl)-amine

To a stirred solution of 2-(3,4-Dihydro-1H-isoquinolin-2yl)-N-(3,3-diphenyl-propyl)-acetamide : INX0052780 (0.184g, 0.047mmol) in tetrahydrofuran (10mL) was added lithium aluminium hydride 1M in Et_2O (Aldrich 21,279-2) (10mL, 10mmol). The reaction mixture was heated at reflux 8h, cooled to room temperature and stirred for 18h. The reaction mixture was quenched with CH_2Cl_2 (30mL) and sodium hydroxide solution (2M, 4mL). The CH_2Cl_2 layer was separated, washed with H_2O dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by preparative HPLC (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H2O-10min. Column: Phenomenex 50 x 19 mm i.d., C18 reverse phase. Flow rate: 15mL/min.), to give the title compound as a pale yellow oil. (0.007g, 3.9%): HPLC retention time 7.76min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 371(M+H).

Example 47: Dibenzyl-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine

Dibenzyl-[2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine was prepared from N,N-Dibenzyl-2-(3,4-dihydro-1H-isoquinolin-2yl)-acetamide and lithium aluminium hydride 1M in Et_2O (Aldrich 21,279-2) according to the method described in Example 46 : HPLC retention time 8.48min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-

95% gradient H2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 357(M+H).

Example 48: 2-(2-Benzyloxy-propyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

To a stirred solution of 2-Benzyloxypropionic acid (0.318g, 1.76mmol) in CH_2Cl_2 (3mL) was added oxalyl chloride (Aldrich O-880-1) (1.12g, 8.83mmol). The reaction mixture was stirred at room temperature for 5h and the solvent and excess reagent removed in vacuo. The residue was dissolved in CH_2Cl_2 (2mL) and added to a stirred solution of 1,2,3,4-Tetrahydro-isoquinolin-8-ol acetate salt (0.367g, 3.52mmol), Et_3N (Aldrich 47,128-3) (0.356g, 3.52mmol) in CH_2Cl_2 (2mL) and the reaction mixture was stirred overnight. The reaction mixture was diluted with 5% hydrochloric acid (5mL), separated and the organic layer washed with H_2O (5mL), brine (5mL), dried, (Na_2SO_4) and the solvent remove in vacuo. The residue (0.147g) was dissolved in tetrahydrofuran (2mL) and Lithium aluminium hydride (Aldrich 21,277-6) (1M in THF, 1mL, 1mmol). The reaction mixture was heated at reflux for 2h, cooled to room temperature and diluted with CH_2Cl_2 (10mL). The mixture was extracted with H_2O (5mL x 2), brine (5mL), dried (Na_2SO_4), filtered and the solvent removed in vacuo. The residue was purified by flash column chromatography to afford the *title compound*as a oil (0.073g, 52%) : HPLC retention time 3.11min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Phenomenex 50 x 4.6 mm i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass Spectrum (ES+) m/z 298 (M+H).

Example 49: 4-Methoxy-1,3-dihydro-1H-isoindole-2-carbothioic acid benzhydryl-amide

2-Benzyl-4-methoxy-2,3-dihydro-2H-isoindole:

2,3-Dimethylanisole (Acros, 15999) (12.5 g, 91.8 mmol), N-bromosuccinimide (Aldrich, B8,125-5) (32.6 g, 183.5 mmol) and benzoyl peroxide (Lancaster, 13174) (300 mg) were refluxed in CCl_4 (200 mL) for 20 hrs. The reaction was cooled and the insoluble material removed by filtration. The solid was washed with CCl_4 and

the combined filtrate concentrated *in vacuo* to afford a yellow solid which was used without further purification. The yellow solid and benzyltriethylammonium chloride (Acros, 16402) (0.75 g, 3.3 mmol) were dissolved in a mixture of 50%aqs NaOH (40 mL) and toluene (175 mL). To the solution was added drop-wise, benzylamine (Aldrich, 18,570-1) (91.8g, 101 mmol) over 15mins at ambient temperature. Once addition was complete, the reaction was stirred for 24hrs at rt. The organic layer was separated, washed with brine (3 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* flash chromatography, eluting with EtOAc/ isohexane (1:15) to afford 2-benzyl-4-methoxy-2,3-dihydro-1H-isoindole as a red oil. Yield 6.5g (30%) : HPLC retention time, 4.21min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 240 (M + H).

4-Methoxy-2,3-dihydro-1H-isoindole:

2-Benzyl-4-methoxy-2,3-dihydro-1H-isoindole (1.9g, 7.94mmol) was dissolved in CH_3OH (50mL) and placed in a 250mL autoclave. 10% Palladium on activated charcoal (Acros, 19503) (300mg) was added and the reaction was hydrogenated at 3.5bar for 24hrs. When complete, the catalyst was separated *via* filtration, and the solvent was removed in vacuo. The residue was purified *via* flash chromatography eluting with $MeOH/CH_2Cl_2$ (1:4) to afford 4-methoxy-2,3-dihydro-1H-isoindole as a beige solid. Yield 0.720g (61%) : HPLC retention time, 3.07min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 150 (M + H).

4-Methoxy-1,3-dihydro-1H-isoindole-2-carbothioic acid benzhydryl-amide

2-Benzyl-4-methoxy-2,3-dihydro-1H-isoindole (50mg, 0.335mmol) and benzhydryl isothiocyanate (Fluorochem, 18194) (75mg, 0.335mmol) were stirred in toluene (2mL) for 24hrs at ambient temperature. The solvent was removed in vacuo and the residue was purified *via* flash chromatography eluting with EtOAc/isohexane (1:4) to afford the *title compoundas* a white solid. Yield 95mg (76%) : HPLC retention time,

4.50min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 375 (M + H).

Example 50: 3,4-Dihydro-1H-isoquinoline-2-carbothioic acid benzhydryl-amide

3,4-Dihydro-1H-isoquinoline-2-carbothioic acid benzhydryl-amide was prepared from 1,2,3,4-tetrahydro-isoquinoline (Aldrich, T1,300-5) (133mg, 1mmol) and benzhydryl isothiocyanate (Fluorochem, 18194) (225mg, 1mmol) according to the method described in Example 49 : HPLC retention time, 4.49min (Solvent: MeCN/ H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 359 (M + H).

Example 51: 3,4-Dihydro-1H-isoquinoline-2-carbothioic acid (2,2-diphenyl-ethyl)-amide

3,4-Dihydro-1H-isoquinoline-2-carbothioic acid (2,2-diphenyl-ethyl)-amide was prepared from 1,2,3,4-tetrahydro-isoquinoline (Aldrich, T1,300-5) (133mg, 1mmol) and 2,2-diphenylethylisothiocyanate (Fluorochem, 8922) (239mg, 1mmol) according to the method described in Example 49 : HPLC retention time, 4.59min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 373 (M + H).

Example 52: 8-Methoxy-3,4-dihydro-1H-isoquinolin-2-carbothioic acid (2,2-diphenyl-ethyl)-amide

8-Methoxy-3,4-dihydro-1H-isoquinolin-2-carbothioic acid (2,2-diphenyl-ethyl)-amide was prepared from 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (82mg, 0.50mmol) and 2,2-diphenylethylisothiocyanate (Fluorochem, 8922) (120mg, 0.50mmol) according to the method described in Example 49 : HPLC retention time, 4.53min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 403 (M + H).

Example 53: 3,4-Dihydro-1H-isoquinoline-2-carbothioic acid benzhydryl-amide

3,4-Dihydro-1H-isoquinoline-2-carbothioic acid benzhydryl-amide was prepared from 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (82mg, 0.50mmol) and benzhydryl isothiocyanate (Fluorochem, 18194) (113mg, 0.50mmol) according to the method described in Example 49 : HPLC retention time, 4.51min (Solvent: MeCN/H_2O/ 0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 389 (M + H).

Example 54: 7-Methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-carbothioic acid benzhydryl-amide

7-Methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-carbothioic acid benzhydryl-amide was prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (50mg, 0.306mmol) [Bioorganic Chemistry (1994), 22(3), 300-317] and benzhydryl isothiocyanate (Fluorochem, 18194) (69mg, 0.306mmol) according to the method described in Example 49 : HPLC retention time, 4.46min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 403 (M + H).

Example 55: 7-Methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-carbothioic acid (2,2-diphenyl-ethyl)-amide

7-Methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-carbothioic acid (2,2-diphenyl-ethyl)-amide was prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (50mg, 0.306mmol) and 2,2-diphenylethylisothiocyanate (Fluorochem, 8922) (73mg, 0.306mmol) according to the method described in Example 49 : HPLC retention time, 4.53min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 417 (M + H).

Example 56: Example 2: N-Benzhydryl-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide

A solution of 2-benzyl-4-methoxy-2,3-dihydro-1H-isoindole (75 mg, 0.50 mmol), K_2CO_3 (69mg, 0.50mmol) and tetrabutylammonium iodide (Aldrich, 14,077-5) (37mg, 0.1mmol) in MeCN (3 mL) was stirred at rt for 30 mins. N-Benzhydryl-2-chloro-acetamide (130 mg, 0.5 mmol) was added and the reaction was refluxed for 5 hrs. The reaction mixture was allowed to cool, diluted with MeCN (5 mL), and the solids removed by filtration. The solvent was removed in vacuo and the residue purified *via* flash chromatography eluting with EtOAc/isohexane (1:2) to afford the *title compound*as a pale green solid. Yield 60 mg (32%) : HPLC retention time, 4.24min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 373 (M + H).

Example 57: N-(2,2-Diphenyl-ethyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide

N-(2,2-Diphenyl-ethyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide was prepared from 2-Benzyl-4-methoxy-2,3-dihydro-1H-isoindole (75mg, 0.50mmol) and 2-chloro-N-(2,2-diphenyl-ethyl)-acetamide (137mg, 0.50mmol) according to the method described in Example 56 : HPLC retention time, 3.10min (Solvent: MeCN/H_2O/0.05% HCOOH, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 387 (M + H).

Example 58: N-(3,3-Diphenyl-propyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide

N-(3,3-Diphenyl-propyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide was prepared from 2-Benzyl-4-methoxy-2,3-dihydro-1H-isoindole (75mg, 0.50mmol) and 2-chloro-N-(3,3-diphenyl-propyl)-acetamide (144mg, 0.50mmol) according to the method described in Example 56 : HPLC retention time, 4.32min (Solvent:

MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 401 (M + H).

Example 59: N-(4,4-Diphenyl-butyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide

N-(4,4-Diphenyl-butyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide was prepared from 2-Benzyl-4-methoxy-2,3-dihydro-1H-isoindole (75mg, 0.50mmol) and 2-chloro-N-(4,4-diphenyl-butyl)-acetamide (151mg, 0.50mmol) according to the method described in Example 56 : HPLC retention time, 4.41min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 415 (M + H).

Example 60: 2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-(2,2-diphenyl-ethyl)-acetamide

2-(3,4-Dihydro-1H-isoquinolin-2-yl)-N-(2,2-diphenyl-ethyl)-acetamide was prepared from 1,2,3,4-tetrahydro-isoquinoline (Aldrich, T1,300-5) (266mg, 2mmol) and 2-chloro-N-(2,2-diphenyl-ethyl)-acetamide (548mg, 2mmol) according to the method described in Example 56 : HPLC retention time, 6.71min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 371 (M + H).

Example 61: N-(2,2-Diphenyl-ethyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(2,2-Diphenyl-ethyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (163mg, 1mmol) (26mg, 2mmol) and 2-chloro-N-(2,2-diphenyl-ethyl)-acetamide (274mg, 1mmol) according to the method described in Example 56 : HPLC retention time, 4.57min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 401 (M + H).

Example 62: 1-(4-benzhydryl-piperazin-1-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

1-(4-Benzhydryl-piperazin-1-yl)-2-chloro-ethanone:

A solution of 1-benzhydryl-piperazine (Acros, 12293) (5.05g, 20mmol) and Et_3N (2.22g, 22mmol) in CH_2Cl_2 (20 mL) was cooled to 5°C using an ice/H2O cooling. Chloroacetyl chloride (Aldrich, 10,449-3) (2.5g, 22mmol) in CH_2Cl_2 (5mL) was added drop wise such that the temperature remained below 20°C. Once addition was complete, the reaction was stirred for for a further 18hrs at ambient temperature. Deionised H2O (50 mL) was added and stirring continued for a further 1hr. The organic layer was separated, washed with brine (3 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to afford 1-(4-benzhydryl-piperazin-1-yl)-2-chloro-ethanone as a brown oil, which was used without further purification. Yield 6.8g (95%) : HPLC retention time, 4.22min (Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 329 (M + H).

1-(4-Benzhydryl-piperazin-1-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone:

1-(4-Benzhydryl-piperazin-1-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (163mg, 1mmol) and 1-(4-benzhydryl-piperazin-1-yl)-2-chloro-ethanone (328mg, 1mmol) according to the method described in Example 55 : HPLC retention time, 4.77min (Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 456 (M + H).

Example 63: 1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-chloro-ethanone:

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-chloro-ethanone was prepared from 1-[bis-(4-fluoro-phenyl)-methyl]-piperazine (Acros, 10018) (5.65g, 20mmol) and chloroacetyl chloride (Aldrich, 10,449-3) (2.5g, 22mmol) according to the method described in Example 62 : HPLC retention time, 4.26min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 365 (M + H).

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone:

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (163mg, 1mmol) and 1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-chloro-ethanone (364mg, 1mmol) according to the method described in Example 55 : HPLC retention time, 4.74min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 492 (M + H).

Example 64: 1-(4-Benzhydryl-piperazin-1-yl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

1-(4-Benzhydryl-piperazin-1-yl)-2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 1,2,3,4-tetrahydro-isoquinoline (Aldrich, T1,300-5) (266mg, 2mmol) and 1-(4-benzhydryl-piperazin-1-yl)-2-chloro-ethanone (658mg, 2mmol) according to the method described in Example 56 : HPLC retention time, 4.71min (Solvent: $MeCN/H_2O/0.05\%$ NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 426 (M + H).

Example 65: 1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 1,2,3,4-tetrahydro-isoquinoline (Aldrich, T1,300-5) (266mg, 2mmol) and 1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-chloro-ethanone (730mg, 2mmol) according to the method described in Example 56 : HPLC retention time, 4.66min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 461 (M + H).

Example 66: 2-(1,3-Dihydro-isoindol-2-yl)-N-(2,2-diphenyl-ethyl)-acetamide

N-(2,2-Diphenyl-ethyl)-2-(4-methoxy-1,3-dihydro-isoindol-2-yl)-acetamide was prepared from isoindoline (Aldrich, 51,557-4) (238mg, 2mmol) and 2-chloro-N-(2,2-diphenyl-ethyl)-acetamide (548mg, 2mmol) according to the method described in Example 56 : HPLC retention time, 4.28min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 357 (M + H).

Example 67: 1-(4-Benzhydryl-piperazin-1-yl)-2-(1,3-dihydro-isoindol-2-yl)-ethanone

1-(4-Benzhydryl-piperazin-1-yl)-2-(1,3-dihydro-isoindol-2-yl)-ethanone was prepared from isoindoline (Aldrich, 51,557-4) (238mg, 2mmol) and 1-(4-benzhydryl-piperazin-1-yl)-2-chloro-ethanone (658mg, 2mmol) according to the method described in Example 56 : HPLC retention time, 4.50min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 412 (M + H).

Example 68: 1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(1,3-dihydro-isoindol-2-yl)-ethanone

1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-(1,3-dihydro-isoindol-2-yl)-ethanone was prepared from isoindoline (Aldrich, 51,557-4) (238mg, 2mmol) and 1-{4-[Bis-(4-fluoro-phenyl)-methyl]-piperazin-1-yl}-2-chloro-ethanone (730mg, 2mmol) according to the method described in Example 56 : HPLC retention time, 4.52min (Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). 1H NMR (400 MHz $(CD_3)_2SO$)□$_H$ 2.20-2.25 (4H),3.40-3.55 (6H), 3.90 (4H), 4.40 (1H), 7.05-7.20 (8H), 7.35-7.45 (4H). Mass spectrum (ES+) m/z 448 (M + H).

Example 69: 2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(phenyl-pyridin-2-yl-methyl)-acetamide

2-Chloro-N-(phenyl-pyridin-2-yl-methyl)-acetamide:

2-Chloro-N-(phenyl-pyridin-2-yl-methyl)-acetamide was prepared from C-phenyl-C-pyridin-2-yl-methylamine hydrochloride (Maybridge, BTB 10358) and chloroacetyl chloride (Aldrich, 10,449-3) (0.282g, 2.5mmol) according to the method described in Example 1 to afford 2-chloro-N-(phenyl-pyridin-2-yl-methyl)-acetamide as a brown solid which was used without further purification. Yield 600mg (98%) : HPLC retention time, 3.40min (Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 261 (M + H).

2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(phenyl-pyridin-2-yl-methyl)-acetamide:

2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-N-(phenyl-pyridin-2-yl-methyl)-acetamide was prepared from 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) and 2-chloro-N-(phenyl-pyridin-2-yl-methyl)-acetamide (130mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time,

4.15min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 388 (M + H).

Example 70: 2-(8-Hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone

2-(2-Nitro-phenoxy)-1-phenyl-ethanone:

A solution of 2-nitrophenol (Aldrich, N1,970-2) (13.9 g, 100 mmol) and K_2CO_3 (15.2 g, 10 mmol) was stirred in MeCN (50 mL) at rt for 30mins. KI (1.83 g, 11 mmol) was added in one portion followed by phenacyl bromide (Lancaster, 6260) (19.9g, 100mmol) in portions. After addition the reaction was stirred for 24hrs at RT, and poured onto ice/H2O (1ltr) with stirring. The solid was separated *via* filtration and washed with H2O. The solid was dried and recrystallized ex IPA (300mL) to afford 2-(2-nitro-phenoxy)-1-phenyl-ethanone as cream coloured crystals. Yield 20g (80%) : HPLC retention time, 3.83min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 258 (M + H).

3-Phenyl-3,4-dihydro-2H-benzo[1,4]oxazine:

To a stirred solution of sodium hypophosphite (Aldrich, 24,366-3) (50g) in deionised H2O (200mL) and THF (200mL) containing 2-(2-nitro-phenoxy)-1-phenyl-ethanone (10g, 39mmol) was added 10% Palladium on activated charcoal (Acros,19503) (1g). The reaction was stirred at RT for 18hrs sodium hypophosphite (Aldrich, 24,366-3) (50g) and 10% Palladium on activated charcoal (Acros,19503) (1g) was added and the reaction was stirred for a further 18hrs at RT. The catalyst was filtered off and the two phase mixture was diluted with deionised H_2O and extracted with Et_2O (x3). The combined extracts were washed with H2O and dried over $MgSO_4$. The solvent was removed in vacuo to afford 3-phenyl-3,4-dihydro-2H-benzo[1,4]oxazine as a red oil which was used without further purification. Yield 8.2g (100%).

2-Chloro-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone:

2-Chloro-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone was prepared from 3-phenyl-3,4-dihydro-2H-benzo[1,4]oxazine (8.2g, 39mmol) and chloroacetyl chloride (Aldrich, 10,449-3) (4.86g, 43mmol) according to the method described in Example 62 : HPLC retention time, 3.91min (Solvent: MeCN/H_2O/0.05% HCOOH; 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.).1H NMR (400 MHz $(CD_3)_2SO$)$\square_H$ 4.45-4.55 (2H), 4.80 (1H), 4.95 (1H), 5.80 (1H), 6.80 (1H), 6.90 (1H), 7.00 (1H), 7.20-7.25 (1H), 7.30-7.35 (4H), 7.80 (1H). Mass spectrum (ES+) m/z 288 (M + H).

2-(8-Hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone:

2-(8-Hydroxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone was prepared from 2-chloro-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone (3.45g, 12mmol) and 1,2,3,4-tetrahydro-isoquinolin-8-ol acetic acid salt (2.51g, 12mmol) according to the method described in Example 56 : HPLC retention time, 6.30min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-10min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.), 1H NMR (400 MHz $(CD_3)_2SO$)$\square_H$ 2.60-2.70 (4H), 3.45-3.65 (4H), 4.35 (1H), 4.90 (1H), 5.95 (1H), 6.50 (1H), 6.55 (1H), 6.75 (1H), 6.85-6.90 (2H), 6.95-7.00 (1H), 7.15 (1H), 7.20-7.30 (4H), 8.00 (1H), 9.30 (1H). Mass spectrum (ES+) m/z 401 (M + H).

Example 71: 2-(8-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone

2-(8-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone was prepared from 2-chloro-1-(3-phenyl-2,3-dihydro-benzo[1,4]oxazin-4-yl)-ethanone (144mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time, 4.49min (Solvent: MeCN/H_2O/0.05% NH_3, 5-

95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 415 (M + H).

Example 72: 2-(8-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-phenoxazin-10-yl-ethanone

2-(8-Methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-1-phenoxazin-10-yl-ethanone was prepared from 2-chloro-1-phenoxazin-10-yl-ethanone (130mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time, 4.53min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 387 (M + H).

Example 73: 1-(10,11-Dihydro-dibenzo[b,f]azepin-5-yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone

1-(10,11-Dihydro-dibenzo[b,f]azepin-5yl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethanone was prepared from 2-chloro-1-(10,11-dihydro-dibenzo[b,f]azepin-5-yl)-ethanone (136mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time, 4.37min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 399 (M + H).

Example 74: N,N-Dibenzyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-Dibenzyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from N,N-dibenzyl-2-chloro-acetamide (137mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time, 4.57min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 401 (M + H).

Example 75 : N,N-Diisopropyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-Diisopropyl-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 2-chloro-N,N-diisopropyl-acetamide (89mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time, 4.26min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 305 (M + H).

Example 76: N-(4,4-Diphenyl-butyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N-(4,4-Diphenyl-butyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 2-chloro-N-(4,4-diphenyl-butyl)-acetamide (151mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 : HPLC retention time, 4.55min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 429 (M + H).

Example 77 : N-(3,3-Diphenyl-propyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propionamide

N-(3,3-Diphenyl-propyl)-2-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propionamide was prepared from 3-chloro-N-(3,3-diphenyl-propyl)-propionamide (151mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 with the following modification: the reaction was refluxed for 24hrs : HPLC retention time, 4.36min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 429 (M + H).

Example 78: N,N-Dibenzyl-3-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propionamide

N,N-Dibenzyl-3-(8-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-propionamide was prepared from N,N-dibenzyl-3-chloro-propionamide (144mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 56 with the following modification: the reaction was refluxed for 24hrs : HPLC retention time, 4.45min (Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 415 (M + H)

Example 79: 2-[3-(2,2-Diphenyl-vinyloxy)-propyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline

1-(3-Bromopropyloxy)-2,2-diphenylethene:

Dipehenyl-acetaldehyde (Aldrich, D20,425-0) (1g, 5.1mmol) was dissolved in $CH2Cl_2$ (10mL) and tetrabutylammonium bromide (Aldrich, 19,311-9) (161mg, 0.5mmol) was added followed by 1.2MNaOH solution (10mL) and 1,3-dibromopropane (Aldrich, 12,590-3) (5.14g, 25.5mmol) with vigorous stirring. The reaction was stirred at RT for 18hrs and acidified with 2M HCl (10mL). The organic phase was separated and washed well with H2O, before being dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified *via* flash chromatography eluting with EtOAc/isohexane (3:97) to afford a colourless oil. Yield 890mg (55%).

2-[3-(2,2-Diphenyl-vinyloxy)-propyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline:

2-[3-(2,2-Diphenyl-vinyloxy)-propyl]-8-methoxy-1,2,3,4-tetrahydro-isoquinoline was prepared from 1-(3-Bromopropyloxy)-2,2-diphenylethene (159mg, 0.5mmol) and 8-methoxy-1,2,3,4-tetrahydro-isoquinoline (81mg, 0.5mmol) according to the method described in Example 55 : HPLC retention time, 5.02min (Solvent: $MeCN/H_2O/0.05\% NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). 1H NMR (400 MHz $CDCl_3$)□$_H$ 2.0 (2H),

2.65-2.70 (4H), 2.85-2.90 (2H), 3.55 (2H), 3.80 (3H), 4.00-4.05 (2H), 6.55 (1H), 6.65 (1H), 6.70 (1H) 7.10 (1H), 7.18-7.24 (4H), 7.25-7.35 (4H), 7.38-7.44 (2H). Mass spectrum (ES+) m/z 400 (M + H)..

Example 80: N-Benzhydryl-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide

N-Benzhydryl-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide was prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (75mg, 0.46mmol) and N-benzhydryl-2-chloro-acetamide (119mg, 0.46mmol) according to the method described in Example 56 : HPLC retention time, 4.40min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 401 (M + H).

Example 81: N-(2,2-Diphenyl-ethyl)2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide

N-(2,2-Diphenyl-ethyl)2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide was prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (75mg, 0.46mmol) and 2-chloro-N-(2,2-diphenyl-ethyl)-acetamide (126mg, 0.46mmol) according to the method described in Example 56 : HPLC retention time, 4.39min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 415 (M + H).

Example 82: N-(3,3-Diphenyl-propyl)2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide

N-(3,3-Diphenyl-propyl)2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide was prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (75mg, 0.46mmol) and 2-chloro-N-(3,3-diphenyl-propyl)-acetamide (132mg, 0.46mmol) according to the method described in Example 56 : HPLC retention time, 4.47min (Solvent: MeCN/H2O/0.05% NH3, 5-95% gradient H2O-6min. Column:

Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 429 (M + H).

Example 83: N,N-Dibenzyl-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide

N,N-Dibenzyl-2-(7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl)-acetamide was prepared from 7-methoxy-2,3,4,5-tetrahydro-1H-benzo[c]azepine (75mg, 0.46mmol) and N,N-dibenzyl-2-chloro-acetamide (126mg, 0.46mmol) according to the method described in Example 56 : HPLC retention time, 4.47min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 415 (M + H).

Example 84: 2-Thiophen-2-ylmethyl-1,2,3,4-tetrahydro-isoquinolin-8-ol

A solution of 1,2,3,4-tetrahydro-isoquinolin-8-ol acetic acid salt (75 mg, 0.358 mmol) and Et_3N (36mg, 0.358mmol) in CH_3OH (2 mL) was stirred at ambient temperature for 30mins. 2-Thiophenecarboxaldehyde (Aldrich T3,240-9) (40mg, 0.358mmol) was added and the reaction was stirred for 2hrs at room temperature. Sodium cyanoborohydride (Aldrich, 15,615-9) (23mg, 0.358mmol) was added and the reaction was stirred at RT for 18hrs. The solvent was removed in vacuo and the residue was purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (2:98) to afford the *title compound*as a white solid. Yield 28mg (32%) : HPLC retention time, 3.43min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). 1H NMR (400 MHz $(CD_3)_2SO$)□$_H$ 2.70-2.75 (2H),2.85-2.90 (2H), 3.60 (2H), 3.95 (2H), 6.50-6.60 (2H), 6.90-6.95 (1H), 6.95-7.0 (1H), 7.05 (1H), 7.35 (1H). Mass spectrum (ES+) m/z 246 (M + H).

Example 85: (1H-Benzoimidazol-5-yl)-(3,4-dihydro-1H-isoquinolin-2-yl)-methanone

To a solution of 5-benzimidazolecarboxylic acid (Aldrich, 29,678-3) (324mg, 2mmol) in CH_2Cl_2/DMF (9:1) (10mL) was added: 1,2,3,4-tetrahydro-isoquinoline (Aldrich, T1,300-5) (320mg, 2.4mmol), Et_3N (404mg, 4mmol), 1-hydroxybenzotriazole (Acros, 16916) (405mg, 3mmol) and 1-[3-(dimethylamino)-propyl]-3-ethyl-carbodiimide (ACT, RC8102) (460mg, 2.4mmol) and the reaction was stirred at RT for 18hrs. The reaction mixture was diluted with EtOAc (10 mL), washed (5% citric acid), (sat. sodium bicarbonate), and (brine). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (5:95) to afford the *title compound*as a brown oil. Yield 15mg (3%) HPLC retention time, 3.09min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 278 (M + H).

Example 86: N-(3,3-Diphenyl-propyl)-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

[2-(4-methoxy-phenyl)-ethyl]-carbamic acid methyl ester:

4-Methoxyphenethylamine (Aldrich, 18,730-5) (25.8g, 171mmol) and Et_3N (20.7g, 205mmol) were dissolved in anhydrous THF (1ltr) and cooled to 0°C. Methyl chloroformate (Aldrich, M3,530-4) 80.8g, 855mmol) was added drop wise keeping the temperature at 0°C. After addition the reaction was stirred at 0°C for a further 2hrs and at RT for 18hrs. Deionised H2O (250mL) was added and the resulting solution was extracted into Et_2O (400mL) and EtOAc (2x300mL). The combined extracts were washed with brine (3x500mL) and 1M HCl (3x400mL). The organic layer was dried over dried $MgSO_4$ and the solvent was removed in vacuo to afford a yellow oil which quickly solidified. This was slurried in isohexane, filtered and washed with isohexane to afford [2-(4-methoxy-phenyl)-ethyl]-carbamic acid methyl ester as a white solid, which was used without further purification. Yield 29g (83%).

7-Methoxy-3,4-dihydro-2H-isoquinolin-1-one:

Phosphorous pentoxide (Fisher, P/3000/53) (14.2g, 50mmol) was added in portions to methanesulphonic acid (Avocado, 13565) (25mL), and the mixture was heated to 130°C. [2-(4-Methoxy-phenyl)-ethyl]-carbamic acid methyl ester (5.23g, 25mmol) was added in portions and the mixture was heated at 140°C for a further 1hr. The reaction was allowed to cool to ca.80°C and it was carefully added to ice with rapid stirring. This solution was extracted with CH_2Cl_2 (3x50mL) and the combined extracts were washed with brine (2x50mL), dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (10:90) to afford 7-methoxy-3,4-dihydro-2H-isoquinolin-1-one. Yield 3.3g (75%). HPLC retention time, 3.41min (Solvent: MeCN/H_2O/0.05% HCOOH, 5-95% gradient H_2O-10min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 178 (M + H).

7-Methoxy-1,2,3,4-tetrahydro-isoquinoline hydrochloride:

Lithium aluminium hydride, 1.0M solution in THF (Aldrich, 21,277-6) (22mL, 22mmol) was added drop wise to 7-methoxy-3,4-dihydro-2H-isoquinolin-1-one (3.0g, 17mmol) in THF (25mL) at RT. After addition the reaction was refluxed for 3hrs. The reaction was cooled to 0°C and quenched by the careful addition of deionised H_2O (1mL), 10% NaOH solution (1mL) and deionised H_2O (3mL). The basic suspension was filtered through celite and extracted into EtOAc (3x150mL). The combined extracts were dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was purified *via* flash chromatography eluting with MeOH/CH_2Cl_2 (10:90) to afford 7-methoxy-1,2,3,4-tetrahydro-isoquinoline. This was dissolved in EtOAc (10mL) and hydrogen chloride, 2.0m solution in Et_2O (Aldrich, 45,518-0) (10mL) was added drop wise, which formed a white ppte. The solid was filtered off and washed with Et_2O to afford 7-methoxy-1,2,3,4-tetrahydro-isoquinoline hydrochloride as a white solid. Yield 1.4g (42%). HPLC retention time, 3.05min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 164 (M + H).

N-(3,3-Diphenyl-propyl)-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide:

7-Methoxy-1,2,3,4-tetrahydro-isoquinoline hydrochloride (200mg, 1mmol) was stirred in MeCN (10mL) with K_2CO_3 (276mg, 2mmol) and TBAI (Aldrich, 14,077-5) (74mg, 0.2mmol) for 30mins. 2-Chloro-N-(3,3-diphenyl-propyl)-acetamide (288mg, 1mmol) was added and the reaction was refluxed for 24hrs. The reaction was cooled, diluted with MeCN (10mL) and the insoluble material was removed *via* filtration. The solvent was removed in vacuo and the residue was purified *via* flash chromatography eluting with EtoAc/isohexane (1:4) to afford the *title compound*as an orange oil. Yield 150mg (36%) HPLC retention time, 4.45min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 415 (M + H).

Example 87: N,N-Dibenzyl-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide

N,N-Dibenzyl-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide was prepared from 7-Methoxy-1,2,3,4-tetrahydro-isoquinoline hydrochloride (200mg, 1mmol) and N,N-dibenzyl-2-chloro-acetamide (274mg, 1mmol) according to the method described in Example 86 : HPLC retention time, 4.53min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 401 (M + H).

Example 88: Dibenzyl-[2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine

Lithium aluminium hydride, 1.0M solution in THF (Aldrich, 21,277-6) (0.42mL, 0.42mmol) was added drop wise to N,N-Dibenzyl-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide (140mg, 0.35mmol). After addition the reaction was refluxed for 3hrs. The reaction was cooled to 0°C and quenched by the careful addition of deionised H_2O (1mL), 10% NaOH solution (1mL) and deionised H_2O (3mL). The basic suspension was filtered through celite and extracted into EtOAc (3x150mL). The combined extracts were dried over $MgSO_4$ and the solvent was

removed in vacuo. The residue was purified *via* flash chromatography eluting with $MeOH/CH_2Cl_2$ (10:90) to afford Dibenzyl-[2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]-amine : HPLC retention time, 5.13min (Solvent: $MeCN/H_2O$/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 387 (M + H).

Example 89: (3,3-Diphenyl-propyl)-[2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]amine

(3,3-Diphenyl-propyl)-[2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-ethyl]amine was prepared from N-(3,3-Diphenyl-propyl)-2-(7-methoxy-3,4-dihydro-1H-isoquinolin-2-yl)-acetamide (130mg, 0.313mmol) and lithium aluminium hydride, 1.0M solution in THF (Aldrich, 21,277-6) (0.375mL, 0.375mmol) according to the method described in Example 88 : HPLC retention time, 4.91min (Solvent: $MeCN/H_2O$/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 401 (M + H).

Example 90: 2-(3,5-Bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-6-ol

A solution of 1,2,3,4-Tetrahydro-isoquinolin-6-ol (0.05 g, 0.13 mmol), 1-bromomethyl-3,5-bis-trifluoromethyl-benzene (0.041 g, 0.13 mmol) and K_2CO_3 (0.018 g, 0.13 mmol) in MeCN (2 mL) was shaken at ambient temperature for 16 hours. The reaction was filtered through a plug of cotton wool, concentrated *in vacuo* and purified by flash chromatography to afford the title compound. HPLC retention time, 1.26 min (Solvent: $MeCN/H_2O$/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 376 (M + H).

Example 91: 2-(2-Chloro-6-fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(2-Chloro-6-fluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 2-chloro-6-fluorobenzyl bromide according

to the method described in Example 90 : HPLC retention time, 0.97 min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 292 (M + H).

Example 92: 2-(2,5-Difluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(2,5-Difluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 2,5-difluorobenzyl bromide according to the method described in Example 90 : HPLC retention time, 1.26 min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 276 (M + H).

Example 93: 2-(3,5-Difluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(3,5-Difluoro-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 3,5-difluorobenzyl bromide according to the method described in Example 90 : HPLC retention time, 0.97 min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 276 (M + H).

Example 94: 2-(4-Trifluoromethylsulfanyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(4-Trifluoromethylsulfanyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 1-bromomethyl-4-trifluoromethylsulphanyl-benzene according to the method described in Example 90 : HPLC retention time, 1.24 min (Solvent: $MeCN/H_2O/0.05\%\ NH_3$, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 340 (M + H).

Example 95: 2-(3,5-Bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-(3,5-Bis-trifluoromethyl-benzyl)-1,2,3,4-tetrahydro-isoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 1-bromomethyl-3,5-bis-trifluoromethyl-benzene according to the method described in Example 90 : HPLC retention time, 1.27 min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 376 (M + H).

Example 96 : 2-[4,4-Bis-(4-fluoro-phenyl)-butyl]-1,2,3,4-tetrahydro-isoquinolin-8-ol

2-[4,4-Bis-(4-fluoro-phenyl)-butyl]-1,2,3,4-tetrahydro-isoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 4,4-Bis-(4-fluoro-phenyl)-bromobutane according to the method described in Example 90 : HPLC retention time, 1.46 min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 394 (M + H).

Example 97 : 2-[4,4-Bis-(4-hydroxy-3,5-dimethyl-phenyl)-pentyl]-1,2,3,4-tetrahydroisoquinolin-8-ol

2-[4,4-Bis-(4-hydroxy-3,5-dimethyl-phenyl)-pentyl]-1,2,3,4-tetrahydroisoquinolin-8-ol was prepared from 1,2,3,4-tetrahydro-isoquinolin-8-ol and 4,4-Bis(4-hydroxy-3,5-dimethyl-phenyl)-bromopentane according to the method described in Example 90 : HPLC retention time, 1.41 min (Solvent: MeCN/H_2O/0.05% NH_3, 5-95% gradient H_2O-6min. Column: Xterra 50 x 4.60 i.d., C18 reverse phase. Flow rate: 1.5mL/min.). Mass spectrum (ES+) m/z 460 (M + H).

Biological Screening

Inhibition of Human $Na_V1.8$ stably expressed in SH-SY-5Y cells

A SH-SY-5Y neuroblastoma cell line stably expressing the human $Na_V1.8$ ($hNa_V1.8$) ion channel was constructed. This cell line has been used to develop a medium to high throughput assay for determining the ability of test compounds to inhibit membrane depolarisation mediated via the $hNa_V1.8$ channel.

SH-SY-5Y $hNa_V1.8$ are grown in adherent monolayer culture using 50:50 Ham's F-12 / EMEM tissue culture medium supplemented with 15% (v/v) foetal bovine serum; 2mM L-glutamine, 1% NEAA and $600\mu g.ml^{-1}$ Geneticin sulphate. Cells are removed from the tissue culture flask using trypsin/EDTA and re-plated into black walled, clear bottom 96-well assay plates at $50{,}000 cells.well^{-1}$ 24 hours prior to assay.

On the day of assay the cell assay plates are washed to remove cell culture medium using a sodium free assay buffer (145mM tetramethyl ammonium chloride; 2mM calcium chloride; 0.8mM magnesium chloride hexahydrate; 10mM HEPES; 10mM glucose; 5mM potassium chloride, pH 7.4). Fluorescent membrane potential dye solution (FLIPR™ membrane potential dye, Molecular Devices Corporation), containing 10μM of a pyrethroid to prevent channel inactivation and 250nM tetrodotoxin (TTX) to reduce interference from TTX-sensitive sodium channels present in the cell line. Test compound, initially dissolved in dimethyl sulfoxide but further diluted in sodium free buffer, is added to achieve the final test concentration range of 100μM – 0.05μM.

Cell plates are incubated for 30 minutes at room temperature to allow equilibration of dye and test compound. Plates are then transferred to a fluorescence plate reader for fluorescence measurement using an excitation wavelength of 530nm whilst measuring fluorescence emission at 565nm. Baseline fluorescence levels are first determined before the addition of a sodium containing buffer (220mM sodium chloride; 2mM calcium chloride; 0.8mM magnesium chloride hexahydrate; 10mM HEPES; 10mM glucose; 5mM potassium chloride. pH 7.4) to cause membrane depolarisation in those cells where channel block has not been effected (final sodium

concentration = 72.5mM). Membrane depolarisation is registered by an increase in fluorescence emission at 565nm.

The change in fluorescence seen in each test well upon the addition of sodium containing buffer is calculated relative to the baseline fluorescence for that well. This figure is then used for calculating the IC_{50} for each test compound. The results are set out in the Table below.

RESULTS

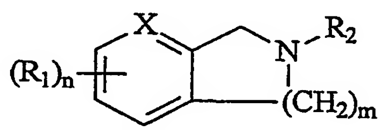
Compound	IC_{50}
Example 91	6.91
Example 92	5.27
Example 93	4.72
Example 94	2.17
Example 95	1.71
Example 8	0.41
Example 70	2.14
Example 48	4.84
Example 11	0.60
Example 14	1.59
Example 16	0.88
Example 17	1.25
Example 18	0.68
Example 19	0.73
Example 21	1.25
Example 22	0.81
Example 23	0.26
Example 24	1.51
Example 25	1.07
Example 26	0.67
Example 27	1.02
Example 45	7.21

Compound	IC_{50}
Example 32	0.23
Example 34	0.19
Example 33	0.86
Example 35	4.86
Example 86	1.46
Example 87	1.10
Example 88	0.58
Example 12	0.99
Example 13	1.39
Example 9	0.43
Example 10	0.48
Example 30	1.59
Example 29	14.96
Example 89	0.49
Example 31	1.85
Example 47	0.47
Example 46	0.29
Example 36	2.80
Example 38	1.39
Example 39	0.45
Example 61	2.56
Example 62	5.63
Example 63	15.84
Example 64	3.14
Example 65	5.64
Example 66	2.05
Example 67	2.35
Example 68	1.95
Example 42	1.05
Example 60	0.95
Example 40	0.97

Compound	IC_{50}
Example 77	0.66
Example 69	8.96
Example 41	7.02
Example 50	2.74
Example 53	4.06
Example 52	4.68
Example 43	1.67
Example 96	1.94
Example 97	1.06

CLAIMS

1. Use of a compound of the formula (I), or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment or prevention of a condition involving sodium ion flux through a sensory neurone specific channel of a sensory neurone



(I)

wherein:

- X is -N- or -CH-;
- n is from 0 to 3;
- each R_1 is the same or different and is a hydroxy, amino, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkylthio, (C_1C_6 alkyl)amino or di(C_1-C_6 alkyl)amino group;
- m is 1, 2 or 3; and
- R_2 is either

(a) -L-A, wherein L is a direct bond or a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety and A is C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group or a 5- to 10- membered heterocyclic group,

(b) -L-CR(A)$_2$ or -L-CH=C(A)$_2$ wherein R is hydrogen or C_1-C_4 alkyl, L is as defined above and each A is the same or different and is as defined above,

(c) -L$'$-Het-A$'$, wherein Het is -O-, -S- or -NR$'$-, A$'$ is -L-A, -L-CR(A)$_2$ or -L-CH=C(A)$_2$, R$'$ is H or -L-A, L$'$ is a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety, L is as defined above, R is as defined above and each A is the same or different and is as defined above,

(d) -L-CO-NR$_3$R$_4$ or -L-CS-NR$_3$R$_4$, wherein L is as defined above and either (i) R_3 and R_4, together with the N atom to which they are attached, form a 5- to 10- membered heteroaryl or heterocyclyl group or (ii) R_3 represents -L-H or A$'$ wherein L and A$'$ are as defined above, and R_4 represents -L$'$-H, -L$'$-CO-A, A$'$, -L-CR(LA)$_2$ or -L-CH=C(LA)$_2$ wherein each L is the same or different,

each A is the same or different, and L', L, R, A and A' are as defined above,

(e) $-CO-L-NR_3R_4$ or $-CS-L-NR_3R_4$ wherein L, R_3 and R_4 are as defined above,

(f) $-CO-A'$ or $-CS-A'$ where A' is as defined above, or

(g) $-L'-O-N=C(A)_2$ or $-CO-L'-O-N=C(A)_2$ wherein L' is as defined above and each A is the same or different and is as defined above,

wherein

- said aryl, carbocyclyl, heteroaryl and heterocyclyl groups are optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6- membered heterocyclyl and heteroaryl groups, and
- said aryl, heteroaryl, carbocyclyl and heterocyclyl groups are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and $-CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 halogen atoms.

2. Use according to claim 1, wherein the aryl, heteroaryl, heterocyclyl and carbocyclyl groups and moieties in the substituents R_1, R_2, R_3 and R_4 are unsubstituted or substituted by 1, 2 or 3 substituents which are the same or different and are selected from halogen, C_1-C_4 alkyl, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and $-CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by one or two halogen atoms.

3. Use according to claim 1 or 2, wherein each R_1 is the same or different and is a hydroxy, halogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio or C_1-C_4 haloalkylthio group.

4. Use according to any one of the preceding claims, wherein each L moiety in the R_2 substituent is the same or different and represents a direct bond or a C_1-C_4 alkyl moiety and/or each L' moiety in the R_2 substituent is the same or different and represents a C_1-C_4 alkyl moiety.

5. Use according to any one of the preceding claims, wherein each A moiety in the R_2 substituent is the same or different and represents a C_6-C_{10} aryl, C_3-C_6 cycloalkyl, 5- or 6- membered heterocyclyl or 5- or 6- membered heteroaryl group, which group is (a) unsubstituted or substituted by 1, 2 or 3 substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and halophenyl substituents and (b) optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6-membered heterocyclyl or heteroaryl groups.

6. Use according to any one of the preceding claims, wherein each R substituent in each -CR(A)$_2$ moiety is the same or different and is hydrogen or methyl.

7. Use according to any one of the preceding claims, wherein each Het moiety in the R_2 substituent is -O-, -S- or -NR$'$- wherein R$'$ is hydrogen, C_1-C_4 alkyl, phenyl or -(C_1-C_4 alkyl)-phenyl.

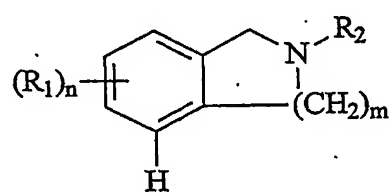
8. Use according to any one of the preceding claims, wherein, when R_3 and R_4, together with the nitrogen atom to which they are attached, form a heterocycle, they form a 5- to 7- membered heterocyclyl group.

9. Use according to claim 8, wherein, when R_3 and R_4, together with the nitrogen atom to which they are attached, form a heterocycle, they form a morpholino, piperazinyl or homopiperindinyl ring, which is (a) unsubstituted or substituted by one or two substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, phenyl and -CHPh$_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by one or two halogen atoms and (b) optionally fused to one or two phenyl rings.

10. Use according to any one of the preceding claims, wherein, when R_3 and R_4 do not together form a heterocycle, R_3 represents hydrogen, C_1-C_4 alkyl or an unsubstituted -(C_1-C_4 alkyl)-phenyl or -(C_1-C_4 alkyl)-CHPh$_2$ group and R_4 represents C_1-C_4 alkyl, A, -(C_1-C_4 alkyl)-A, -(CH$_2$)$_m$-CH(A)$_2$, -CH[(CH$_2$)$_m$A]$_2$ or -(CH$_2$)$_m$-CO-A wherein each A is the same or different and is as defined above and

m is 0, 1, 2, 3 or 4, the A moieties in the R_4 substituent being (a) unsubstituted or substituted by one or two substituents selected from C_1-C_4 alkyl, C_1-C_4 alkoxy, halogen, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy and C_1-C_2 haloalkylthio substituents and (b) monocyclic or fused to one or two phenyl rings.

11. Use according to any one of the preceding claims, wherein the compound of formula (I) is a compound of formula (Ia):



(Ia)

wherein

- n is 0 or 1;
- each R_1 is the same or different and is C_1-C_2 alkyl, hydroxy or C_1-C_2 alkoxy;
- m is 1, 2 or 3; and
- R_2 is either

(a) -L-A wherein L represents a direct bond or a C_1-C_4 alkyl moiety and A is a phenyl, thienyl, triazolyl, pyridyl, fluorenyl, thiazolyl, tetrahydroisoquinolinyl or benzimidazolyl group, which group is unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_2 alkyl, hydroxy, C_1-C_2 alkoxy, C_1-C_2 haloalkyl, C_1-C_2 haloalkoxy, C_1-C_2 haloalkylthio and phenyl substituents,

(b) -L-CR(A)$_2$ or -L-CH=C(A)$_2$ wherein R is hydrogen or methyl, L is as defined above and each A is the same or different and is as defined above,

(c) -L$'$-Het-A$'$ wherein Het is -O- or -NR$'$- wherein R$'$ is hydrogen, C_1-C_4 alkyl or benzyl, A$'$ is -L-A, -L-CR(A)$_2$ or -L-CH=C(A)$_2$, L$'$ is a C_1-C_4 alkyl moiety, L is as defined above, R is as defined above and each A is the same or different and is as defined above,

(d) -L-CO-NR$_3$R$_4$ wherein L is as defined above and either (i) R_3 and R_4, together with the nitrogen atom to which they are attached, form a morpholino, piperazinyl or homopiperidinyl ring which is (a) substituted or

unsubstituted by one or two substituents selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, phenyl and $-CHPh_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by one or two halogen atoms and (b) optionally fused to one or two phenyl rings, or (ii) R_3 represents hydrogen, C_1-C_4 alkyl or an unsubstituted benzyl or $-CH_2-CH_2-CHPh_2$ group and R_4 represents C_1-C_4 alkyl, fluorenyl, -(C_1-C_4 alkyl)-phenyl, -(C_1-C_4 alkyl)-(5- to 6- membered heteroaryl), $-(CH_2)_m-CHA''A'''$ where m is 0, 1, 2 or 3 and A'' and A''' are the same or different and each represent phenyl or a 5- or 6- membered heteroaryl group, $-CH[(CH_2)_nPh]_2$, wherein n is 0, 1 or 2, or $-(CH_2)_p-CO-R$ wherein p is 1, 2 or 3 and R is 5- or 6- membered heterocyclic group fused to a phenyl ring, the cyclic moieties in said R_4 groups being unsubstituted or substituted by a halogen atom, C_1-C_2 alkyl or C_1-C_2 alkoxy group,

(e) $-CO-L-NR_3R_4$ or $-CS-L-NR_3R_4$ wherein L, R_3 and R_4 are as defined above,

(f) $-CO-A'$ or $CS-A'$ wherein A' is as defined above, or

(g) $-CO-L'-O-N{=}C(A)_2$ wherein L' is as defined above and each A is the same or different and is as defined above.

12. A compound of the formula (I), as defined in any one of the preceding claims, or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a compound of the formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

14. A composition according to claim 13 which is a capsule or tablet comprising from 10 to 500 mg of a compound of the formula (I), as defined in any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

15. An inhalation device comprising a pharmaceutical composition according to claim 14.

16. An inhalation device according to claim 15 which is a nebulizer.

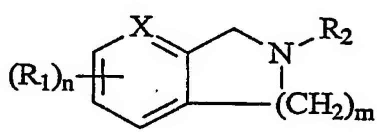
17. A compound according to any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, for use in the treatment of the human or animal body.

18. A method of treating a patient suffering from or susceptible to a condition mediated by SNS sodium channels, which method comprises administering to said patient an effective amount of a compound of formula (I), as defined in any of claims 1 to 11, or a pharmaceutically acceptable salt thereof.

ABSTRACT

CHEMICAL COMPOUNDS

Compounds of the formula (I), and pharmaceutically acceptable salts thereof, are found to be antagonists of SNS sodium channels. They are therefore useful as analgesic and neuroprotective agents



(I)

wherein:

- X is -N- or -CH-;
- n is from 0 to 3;
- each R_1 is the same or different and is a hydroxy, amino, halogen, C_1-C_6 alkyl, C_1-C_6 haloalkyl, C_1-C_6 alkoxy, C_1-C_6 haloalkoxy, C_1-C_6 alkylthio, C_1-C_6 haloalkylthio, (C_1C_6 alkyl)amino or di(C_1-C_6 alkyl)amino group;
- m is 1, 2 or 3; and
- R_2 is either

(h) -L-A, wherein L is a direct bond or a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety and A is C_6-C_{10} aryl, C_3-C_6 carbocyclyl, a 5- to 10- membered heteroaryl group or a 5- to 10- membered heterocyclic group,

(i) -L-CR(A)$_2$ or -L-CH=C(A)$_2$ wherein R is hydrogen or C_1-C_4 alkyl, L is as defined above and each A is the same or different and is as defined above,

(j) -L′-Het-A′, wherein Het is -O-, -S- or -NR′-, A′ is -L-A, -L-CR(A)$_2$ or -L-CH=C(A)$_2$, R′ is H or -L-A, L′ is a C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl moiety, L is as defined above, R is as defined above and each A is the same or different and is as defined above,

(k) -L-CO-NR$_3$R$_4$ or -L-CS-NR$_3$R$_4$, wherein L is as defined above and either (i) R_3 and R_4, together with the N atom to which they are attached, form a 5- to 10- membered heteroaryl or heterocyclyl group or (ii) R_3 represents -L-H or A′ wherein L and A′ are as defined above, and R_4 represents -L′-H, -L′-CO-A,

A', -L-CR(LA)$_2$ or -L-CH=C(LA)$_2$ wherein each L is the same or different, each A is the same or different, and L', L, R, A and A' are as defined above,

(l) -CO-L-NR$_3$R$_4$ or -CS-L-NR$_3$R$_4$ wherein L, R$_3$ and R$_4$ are as defined above,

(m) -CO-A' or -CS-A' where A' is as defined above, or

(n) -L'-O-N=C(A)$_2$ or -CO-L'-O-N=C(A)$_2$ wherein L' is as defined above and each A is the same or different and is as defined above,

wherein

- said aryl, carbocyclyl, heteroaryl and heterocyclyl groups are optionally fused to one or two cyclic moieties selected from phenyl rings and 5- to 6- membered heterocyclyl and heteroaryl groups, and
- said aryl, heteroaryl, carbocyclyl and heterocyclyl groups are unsubstituted or are substituted by 1, 2 or 3 substituents which are the same or different and are selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, halogen, hydroxy, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_1-C_4 alkylthio, C_1-C_4 haloalkylthio, phenyl and -CHPh$_2$ substituents, the phenyl moieties in said substituents being unsubstituted or substituted by 1 or 2 halogen atoms.

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